

TITLE: METAL CATALYSTS AND METHODS
FOR MAKING AND USING SAME

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METAL CATALYSTS AND METHODS FOR MAKING AND USING SAME

The present application claims the benefit of
U.S. Provisional Patent Application Serial No.
5 60/131,262, filed April 27, 1999.

The present invention was made with the support
of the National Science Foundation Contract No. CHE
9726124 and National Institutes of Health Contract Nos.
DA06301 and DA05886. The Federal Government may have
10 certain rights in this invention.

FIELD OF THE INVENTION

The present invention relates to metal
catalysts and, more particularly, to bis transition metal
15 catalysts and to methods for making and using same.

BACKGROUND OF THE INVENTION

Catalysts

In recent years, it has become widely
recognized that ligands having C_2 symmetry can be used
20 with great effect in the design of catalysts for
asymmetric synthesis. Several reviews have addressed the
use of such catalysts in asymmetric carbenoid reactions.
These include: Singh et al., "Catalytic Enantioselective
Cyclopropanation of Olefins Using Carbenoid Chemistry,"
25 Synthesis, 1997:137-149 and Doyle, Chiral catalysts for
Enantioselective Carbenoid Cyclopropanation Reactions,"
Recl. Trav. Chim. Pays-Bas, 110:305-316 (1991). The use

of these catalysts in asymmetric transformations has also been reported in Pfaltz, "Chiral Semicorrins and Related Nitrogen Heterocycles as Ligands in Asymmetric Catalysts," Acc. Chem. Res., 26:339-345 (1993); Noyori, 5 Asymmetric Catalysis in Organic Synthesis, New York: John Wiley & Sons, Inc., pp. 16-95 (1994); Evans et al., "Bis(oxazoline)-copper Complexes as Chiral Catalysts for the Asymmetric Aziridination of Olefins," J. Am. Chem. Soc., 115:3328-3329 (1993); Li et al., "Asymmetric 10 Alkene Aziridination With Readily Available Chiral Diimine-based Catalysts," J. Am. Chem. Soc., 115:5326-5327 (1993); Nishikori et al., "Catalytic and Highly Enantioselective Aziridination of Styrene Derivatives," Tetrahedron Lett., 37:9245-9248 (1996); Nicholas et al., 15 "On the Mechanism of Allylic Amination Catalyzed by Iron Salts," J. Am. Chem. Soc., 119:3302-3310 (1997); Johnson et al., "Catalytic Asymmetric Epoxidation of Allylic Alcohols," in Ojima, ed., Catalytic Asymmetric Synthesis, New York: VCH Publishers, Inc., pp. 103-158 (1993); and 20 Jacobsen, "Asymmetric Catalytic Epoxidation of Unfunctionalized Olefins," in Ojima, ed., Catalytic Asymmetric Synthesis, New York: VCH Publishers, Inc., pp. 159-202 (1993). The C_2 symmetry of a complex cuts in half the number of possible arrangements that are 25 available for the reacting substrate or substrates. Consequently, it becomes much easier to design a catalyst with well-defined chiral influence to effect high asymmetric induction of the reaction in question. A natural extension for chiral catalyst design would be to 30 move from complexes having C_2 symmetry to complexes having D_2 symmetry. Catalysts having D_2 symmetry would cut to a quarter the number of possible arrangements that are available for the reacting substrate or substrates

and, thus, would have the potential of being very reliable chiral catalysts.

Even though the concept of using catalysts having D_2 symmetry is a very attractive proposition, the practical outcome of trying to develop such catalysts has not had much success. The general strategy, such as that described in Maxwell et al., "Shape-selective and Asymmetric Cyclopropanation of Alkenes Catalyzed by Rhodium Porphyrins," Organometallics, 11:645-652 (1992) ("Maxwell"), Morice et al., "Oxidation and Chiral Recognition of Amino Esters by Dioxoruthenium(VI) Porphyrins: Synthesis of a New Imino Ester Ru(II) Complexes," Tetrahedron Lett., 37:6701-6704 (1996), and Halterman et al., "Synthesis of D_2 -symmetric Benzaldehydes and Achiral Arylsipyrromethanes," Tetrahedron Lett., 37:6291-6294 (1996), has been to develop very elaborate D_2 ligands built around a porphyrin core. However, the synthetic procedures for these ligands are long and give poor yields, and the resulting chiral catalysts perform only with moderate asymmetric induction. Maxwell suggests that one problem with these porphyrin complexes is that the chiral influence is too far removed from the metal center to be very effective in asymmetric induction.

In view of the unrealized promise of catalysts having D_2 symmetry, there is a need for catalysts having D_2 symmetry which are easily to produce and which have high asymmetric inductive effects. The present invention, in part, is directed to meeting this need.

30 Synthesis of Gem-Diarylalkyl Derivatives

The gem-diarylalkyl group is present in a number of important pharmaceuticals, such as tolterodine, CDP-840, and nomifensine, and sertraline. Consequently,

a number of reports have recently appeared describing methods for the asymmetric synthesis of gem-diarylalkyl derivatives. These include: Frey et al., J. Org. Chem., 63:3120-3124 (1998) ("Frey"); Andersson et al., J. Org. Chem., 63:8067-8070 (1998) ("Andersson"); Houpis et al., Tetrahedron Lett., 38:7131-7134 (1997) ("Houpis"); Christenson et al., Tetrahedron, 47:4739-4752 (1991) ("Christenson"); Alexakis et al., Tetrahedron Lett., 29:4411-4414 (1988) ("Alexakis"); and Corey et al., Tetrahedron Lett., 35:5373-5376 (1994) ("Corey"). Particularly effective have been the asymmetric conjugate addition of organometallic reagents to cinnamates, described in Frey, Andersson, Houpis, Christenson, and Alexakis, and the aryl cuprate addition to enantiomerically pure dimethyl 2-phenylcyclopropane-1,1-dicarboxylate, described in Corey. However, these reaction schemes involve multiple steps with poor overall yields and inconsistent chiral purity.

Accordingly, a need continues to exist for methods for preparing asymmetric gem-diarylalkyl derivatives. The present invention, in part, is directed to meeting this need.

Formation of Carbon-Carbon Bonds

The aldol reaction is a central transformation in organic synthesis. See, for example, Heathcock in Morrison, ed., Asymmetric Synthesis, San Diego: Academic Press, Vol. 3, Chapter 2 (1984) ("Heathcock"). Not only is the reaction a powerful carbon-carbon bond forming process, but, also, Heathcock reports that the reaction can be made highly diastereoselective by using enolates of defined geometry. Furthermore, high enantioselectivity can be achieved by using chiral auxiliaries (Heathcock) or by using chiral catalysts.

The use of chiral catalysts in enantioselective aldol reactions has been recently reviewed in Nelson, "Catalyzed Enantioselective Aldol Additions of Latent Enolate Equivalents," Tetrahedron-Asymmetry, 9:357-389 (1998). Of particular interest are aldol reactions between enolates of arylacetates and aldehydes. For example, Evans et al., "C-2-symmetric Copper(II) Complexes as Chiral Lewis Acids. Scope and Mechanism of the Catalytic Enantioselective Aldol Additions of Enolsilanes to Pyruvate Salts," J. Am. Chem. Soc., 121:669-699 (1999), recently reported a reaction between a silylketene acetal of phenylacetate and benzyloxyacetaldehyde using a Cu(II) bisoxazoline complex. The reaction resulted in low enantioselectivity (about 9 %) and no diastereoselectivity. However, better asymmetric induction has been achieved in such aldol reactions by using chiral enolates (Lutzen et al., "D-xylose Derived Oxazolidin-2-ones as Chiral Auxiliaries in Stereoselective Aldol Reactions," Tetrahedron-Asymmetry, 8:1193-1206 (1997)). However, processes of this type occurring in high yields and with good diastereoselectivity and enantioselectivity has not been reported.

Accordingly, a need continues to exist for methods for forming carbon-carbon bonds with good diastereoselectivity and enantioselectivity. The present invention, in part, is directed to meeting this need.

RITALIN™ and its Congeners

Attention Deficit Disorder ("ADD") is the most commonly diagnosed illness in children. Symptoms of ADD include distractibility and impulsivity. A related disorder, termed Attention Deficit Hyperactivity Disorder ("ADHD"), is further characterized by increased symptoms

of hyperactivity in patients. Racemic methylphenidate (e.g., RITALIN™) is a mild central nervous system stimulant, with pharmacological activity qualitatively similar to amphetamines, and has been the drug of choice for symptomatic treatment of ADD in children. Current administration of racemic methylphenidate, however, results in notable side effects, such as anorexia, weight loss, insomnia, dizziness, and dysphoria. Additionally, racemic methylphenidate, which is a Schedule II controlled substance, produces a euphoric effect when administered intravenously or through inhalation and, thus, carries a high potential for substance abuse in patients.

At least 70% individuals who are infected with the Human Immunodeficiency Virus ("HIV") who have developed Acquired Immunodeficiency Syndrome ("AIDS") eventually manifest cognitive defects, and many display signs and symptoms of dementia. Complaints of forgetfulness, loss of concentration, fatigue, depression, loss of attentiveness, mood swings, personality change, and thought disturbance are common in patients with HIV disease. Racemic methylphenidate has been used to treat cognitive decline in AIDS patients. As described above, racemic methylphenidate, which is a Schedule II controlled substance, produces a euphoric effect when administered intravenously or through inhalation, and thus carries a high potential for drug abuse in AIDS patients.

Glutathione is an important antioxidative agent that protects the body against electrophilic reactive compounds and intracellular oxidants. It has been postulated that HIV-AIDS patients suffer from drug hypersensitivity due to drug overload and an acquired glutathione deficiency. Patients with HIV infection have

demonstrated a reduced concentration of glutathione in plasma, cells, and broncho-alveolar lavage fluid. Clinical data suggest that HIV-seropositive individuals display adverse reactions to the simultaneous
5 administration of several otherwise therapeutic drugs. It is therefore desirable to provide for the administration of methylphenidate in reduced dosages among patients with drug hypersensitivity due to HIV infection.

10 Methylphenidate possesses two centers of chirality and thus can exist as four separate stereoisomers. Diastereomers are known in the art to possess differing physical properties, such as melting point and boiling point. For example, while the *threo*-
15 racemate of methylphenidate produces the desired effect on the central nervous system, the *erythro*-racemate contributes to hypertensive side-effects and exhibits lethality in rats.

Additional studies in animals, children and
20 adults have demonstrated pharmacological activity in the *d-threo* isomer of methylphenidate (2R:2'R). Although the role of the *l-threo* isomer in toxicity or adverse side effects has not been thoroughly examined, the potential for isomer ballast in methylphenidate is of concern for
25 many patients, particularly those drug hypersensitive patients described above.

Although *l-threo*-methylphenidate is rapidly and stereo-selectively metabolized upon oral administration, intravenous administration or inhalation results in high
30 *l-threo*-methylphenidate serum levels. Intravenous administration and inhalation are the methods of choice by drug abusers of current methylphenidate formulations, and it has been postulated that the euphoric effect

produced by current formulations of methylphenidate is due to the action of the l-threo-methylphenidate.

Accordingly, it has been suggested that the use of the d-threo isomer (2R:2'R) of methylphenidate which is substantially free of the l-threo isomer produces high methylphenidate activity levels and simultaneously reduces methylphenidate's euphoric effect and the potential for abuse among patients.

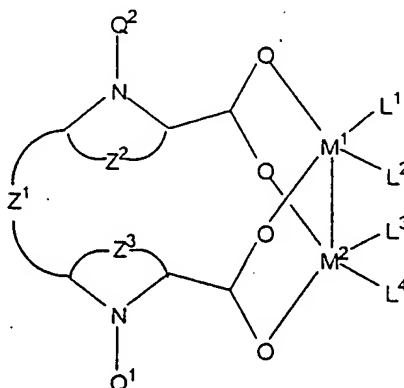
Methods for synthesizing d-threo methylphenidate have been reported. However, these methods involve long, complicated syntheses, have poor overall yields, and require at least some separation of mixtures of enantiomers and/or diastereomers.

In view of the advantages of pure d-threo methylphenidate and the deficiency in the art of methods for making this compound and its congeners, a need exists for an improved synthetic method for making pure d-threo methylphenidate and its congeners. The present invention, in part, is directed to meeting this need.

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SUMMARY OF THE INVENTION

The present invention relates to a compound having the formula:

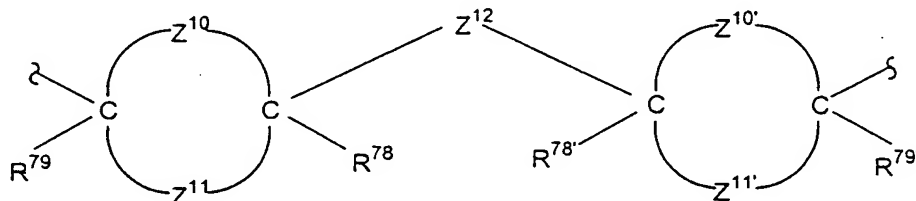


wherein M¹ and M² are the same or different and are transition metal atoms or ions; Z² and Z³, independently,

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are the atoms necessary to complete a 3-12 membered heterocyclic ring; Z^1 is an alkylene or arylene group; Q^1 and Q^2 are the same or different and are electron withdrawing groups; L^1 and L^3 , taken together, represent
 5 -O-CR¹³-O-; L^2 and L^4 , taken together, represent -O-CR¹⁴-O-; and R^{13} and R^{14} are the same or different and are selected from the group consisting of alkyl groups and aryl groups or R^{13} and R^{14} represent alkylene or arylene groups that are directly or indirectly bonded to one
 10 another.

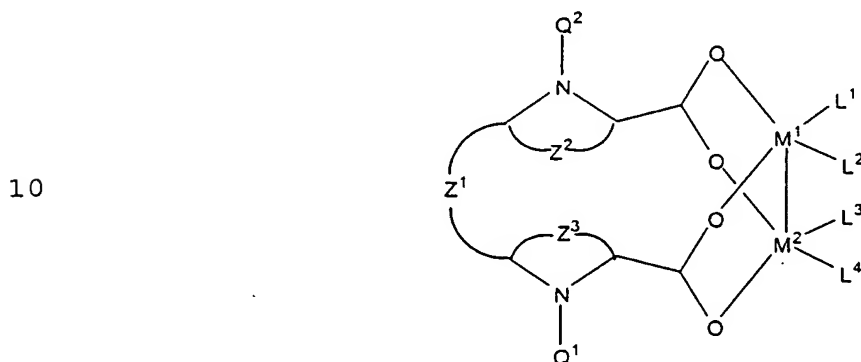
The present invention also relates to a compound which includes a first metal atom and a second metal atom that are bonded to one another along an axis and two carboxylate ligands. Each of the two carboxylate
 15 ligands includes two carboxylate groups bonded to each other via a moiety having the formula:



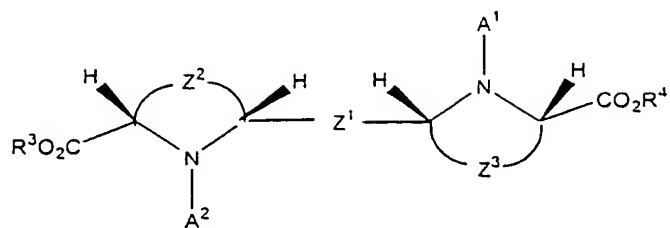
where Z^{10} and Z^{11} , together with the atoms to which they are bonded form a 3-12 membered ring; $Z^{10'}$ and $Z^{11'}$,
 20 together with the atoms to which they are bonded form a 3-12 membered ring; and R^{78} , $R^{78'}$, R^{79} , and $R^{79'}$ are independently selected from the group consisting of H, an alkyl group, and an aryl group. Z^{12} is an alkylene or arylene group. Each of the two carboxylate groups
 25 includes a first carboxylate oxygen atom (" O^1 "), a second carboxylate oxygen atom (" O^2 "), and a carbon (" C ") to which the O^1 and the O^2 are bonded thereby forming two O^1 -C- O^2 moieties, and each O^1 -C- O^2 moiety defines a plane which is substantially parallel to the axis. O^1 of each

of the two carboxylate groups of each of the two carboxylate ligands is bonded to the first metal atom, and O² of each of the two carboxylate groups of each of the two carboxylate ligands is bonded to the second metal atom.
 5 Each of the two carboxylate ligands further includes at least two chiral centers, and the compound has D₂ symmetry.

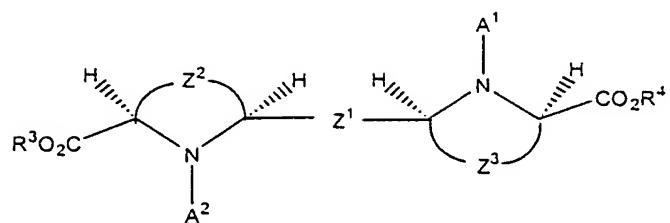
The present invention also relates to a method for making a compound having the formula:



wherein M¹ and M² are the same or different and are transition metal atoms or ions; Z² and Z³, independently, are the atoms necessary to complete a 3-12 membered heterocyclic ring; Z¹ is an alkylene or arylene group; Q¹
 15 and Q² are the same or different and are electron withdrawing groups; L¹ and L³, taken together, represent -O-CHR¹³-O-; L² and L⁴, taken together, represent -O-CHR¹⁴-O-; and R¹³ and R¹⁴ are the same or different and are selected from the group consisting of alkyl groups
 20 and aryl groups or R¹³ and R¹⁴ represent alkylene or arylene groups that are directly or indirectly bonded to one another. The method includes providing a ligand having the formula:

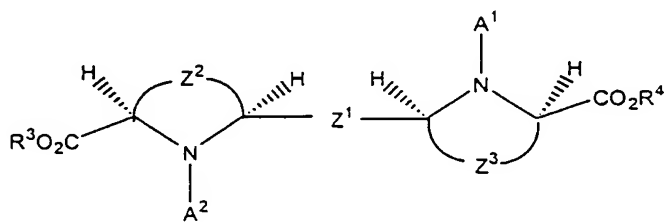


or



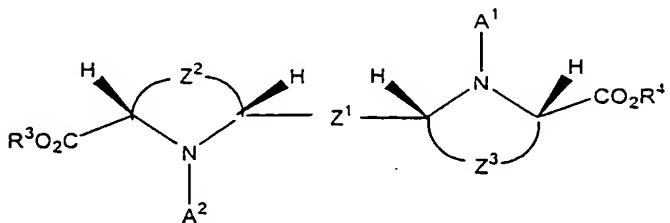
or a mixture thereof, wherein each of A¹ and A² is
 5 independently selected from the group consisting of a
 hydrogen atom and an electron withdrawing group and
 wherein each of R³ and R⁴ is independently selected from
 the group consisting of H, alkyl, and aryl. The method
 further includes converting the ligand with a bis-metal
 10 salt under conditions effective to produce the compound.

The present invention also relates to compounds
 having one of the following formulae:



or

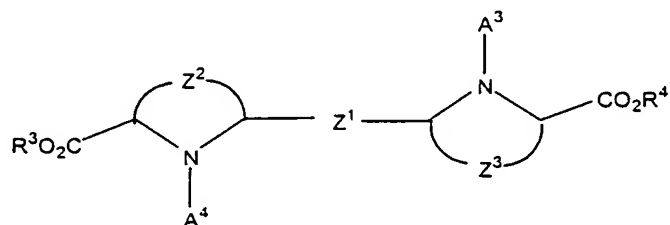
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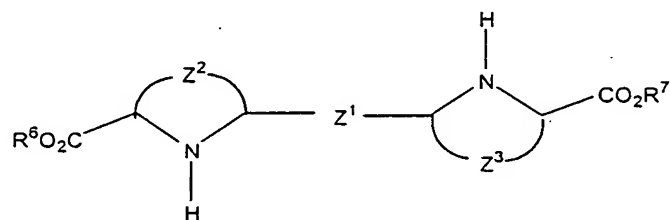
wherein Z² and Z³, independently, are the atoms necessary
 to complete a 3-12 membered heterocyclic ring; Z¹ is an

alkylene or arylene group; A¹ and A² are independently selected from the group consisting of a hydrogen atom and an electron withdrawing group; and each each of R³ and R⁴ is independently selected from the group consisting of
5 H, alkyl, and aryl.

The present invention also relates to a method for preparing an N-substituted compound having the formula:

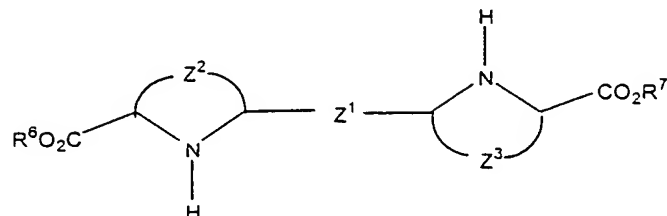


10 wherein Z² and Z³, independently, are the atoms necessary to complete a 3-12 membered heterocyclic ring; Z¹ is an alkylene or arylene group; A³ and A⁴ are the same or different and are electron withdrawing groups having the formulae -C(O)R², -SO₂R², or -P(O)R²R^{2'}; each of R¹, R^{1'}, R²,
15 and R^{2'} is an alkyl group, an aryl group, or an alkoxy group; and each of R³ and R⁴ is independently selected from the group consisting of H, alkyl, and aryl. The method includes providing an N-unsubstituted compound having the formula:

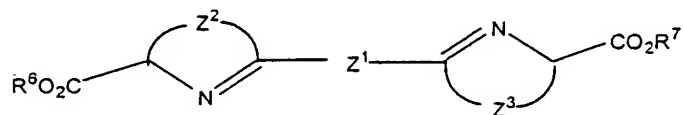


20 wherein each of R⁶ and R⁷ is independently selected from an alkyl group or an aryl group. The method further includes converting the N-unsubstituted compound to the N-substituted compound with an acylating agent, a
25 sulfonylating agent, or a phosphorylating agent.

The present invention also relates to a method for preparing an N-unsubstituted compound having the formula:

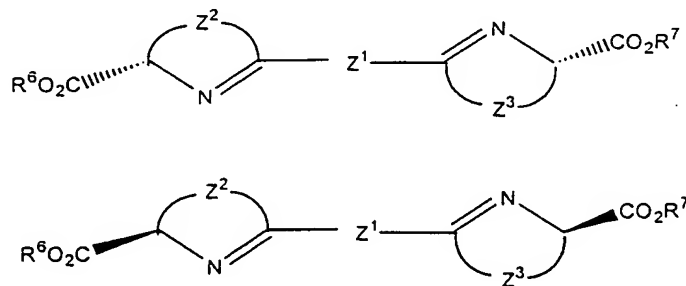


5 wherein Z² and Z³, independently, are the atoms necessary to complete a 3-12 membered heterocyclic ring; Z¹ is an alkylene or arylene group; and R⁶ and R⁷ are independently selected from an alkyl group or an aryl group. The method includes providing an unsaturated
10 heterocyclic compound having the formula:



and converting the unsaturated heterocyclic compound to the N-unsubstituted compound using hydrogenation.

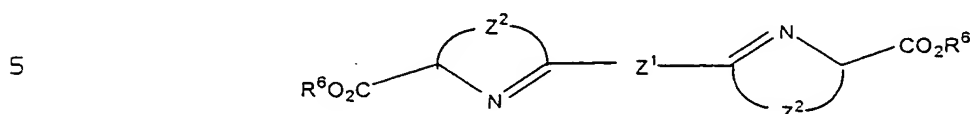
The present invention, in still another
15 embodiment thereof, relates to a compound having one of the following formulae:



20 wherein Z² and Z³, independently, are the atoms necessary to complete a 3-12 membered heterocyclic ring; Z¹ is an alkylene or arylene group; and R⁶ and R⁷ are

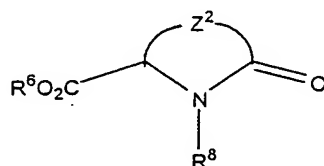
independently selected from an alkyl group or an aryl group.

The present invention also relates to a method for preparing an unsaturated heterocyclic compound having the formula:



wherein Z² represents the atoms necessary to complete a 3-12 membered heterocyclic ring; Z¹ is an alkylene or arylene group; and R⁶ is selected from an alkyl group or an aryl group. The method includes providing a cyclic

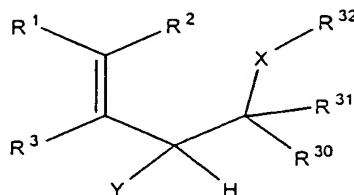
10 ketone having the formula:



wherein R⁸ is an amine-protecting group. The method further includes converting the cyclic ketone to the N-unsaturated heterocyclic compound with a bis-lithium

15 compound having the formula Z¹Li₂.

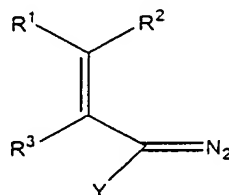
The present invention further relates to a method of producing a compound having the formula:



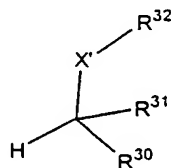
where R¹, R², and R³ are independently selected from H, alkyl, aryl, or vinyl or where R¹ and R³, together with the atoms to which they are bonded, form a 5-12 membered ring; Y is an electron withdrawing group; X is CH₂, O, or NR¹¹; R¹¹ is H, an alkyl group, an aryl group, an acyl

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group, an alkoxy carbonyl group, or a silyl group having the formula $-\text{SiR}^{33}\text{R}^{34}\text{R}^{35}$; each of R^{30} and R^{31} is independently selected from the group consisting of H, alkyl, aryl, and vinyl; R^{32} is an alkyl group, an aryl group, an acyl group, an alkoxy carbonyl group, or a silyl group having the formula $-\text{SiR}^{36}\text{R}^{37}\text{R}^{38}$; or R^{31} and R^{32} , together with the atoms to which they are bonded, form a 5-12 membered ring; R^{33} , R^{34} , R^{35} , R^{36} , R^{37} , and R^{38} are independently selected from an alkyl group and an aryl group; provided that when each of R^{30} and R^{31} is H, X is not CH_2 . The method includes providing a diazo compound having the formula:

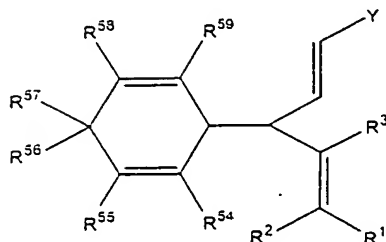


and converting the diazo compound with a compound having the formula:

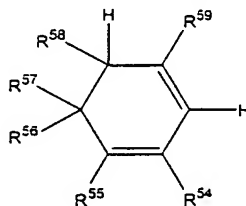


in the presence of a bis-transition metal catalyst, under conditions effective to produce the compound. In the immediately preceding formula, X' is CH_2 , O, or $\text{NR}^{11'}$ and $\text{R}^{11'}$ is an alkyl group, an aryl group, an acyl group, an alkoxy carbonyl group, or a silyl group. When X is O or CH_2 , when R^1 and R^3 , together with the atoms to which they are bonded, form a 5-12 membered ring, and when R^{31} and R^{32} , together with the atoms to which they are bonded, form a 5-12 membered ring, conversion of the diazo compound is carried out substantially in the absence of oxygen.

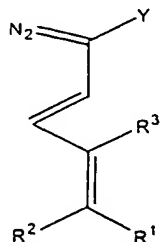
In yet another embodiment, the present invention relates to a method for producing a compound having the formula:



5 wherein R^1 , R^2 , and R^3 are independently selected from H, an alkyl group, an aryl group, or a vinyl group or where R^1 and R^3 , together with the atoms to which they are bonded, form a 5-12 membered ring; Y is an electron withdrawing group; and R^{54} , R^{55} , R^{56} , R^{57} , R^{58} , and R^{59} are
10 independently selected from the group consisting of H, alkyl, aryl, halogen, and alkoxy. The method includes providing a 1,3-cyclohexadiene having the formula:

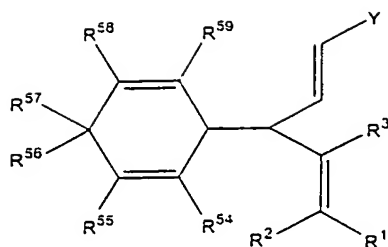


The method further includes converting the 1,3-
15 cyclohexadiene with a diazo compound having the formula:



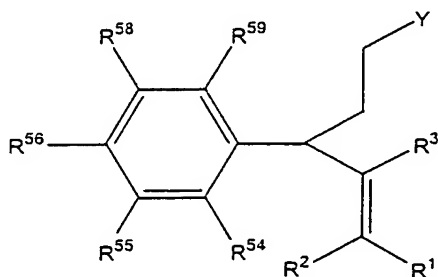
in the presence of a bis-transition metal catalyst and under conditions effective to produce the compound.

The present invention also relates to a
20 compound having the formula:

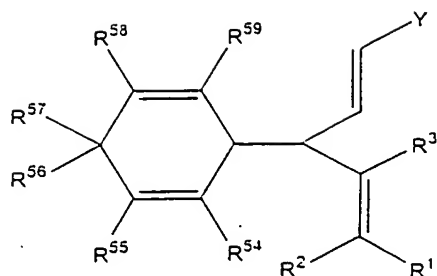


R¹, R², and R³ are independently selected from H, an alkyl group, an aryl group, or a vinyl group, or R¹ and R³, together with the atoms to which they are bonded, form a
 5 5-12 membered ring. Y is an electron withdrawing group. R⁵⁴, R⁵⁵, R⁵⁶, R⁵⁷, R⁵⁸, and R⁵⁹ are independently selected from the group consisting of H, alkyl, aryl, halogen, and alkoxy.

In still another embodiment, the present
 10 invention relates to a method for making a compound having the formula:

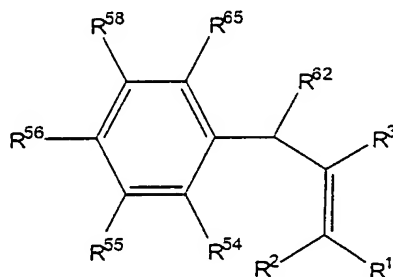


in which R¹, R², and R³ are independently selected from H, an alkyl group, an aryl group, or a vinyl group or where
 15 R¹ and R³, together with the atoms to which they are bonded, form a 5-12 membered ring; Y is an electron withdrawing group; and R⁵⁴, R⁵⁵, R⁵⁶, R⁵⁸, and R⁵⁹ are independently selected from the group consisting of H, alkyl, aryl, halogen, and alkoxy. The method includes
 20 providing a cyclohexadiene derivative having the formula:

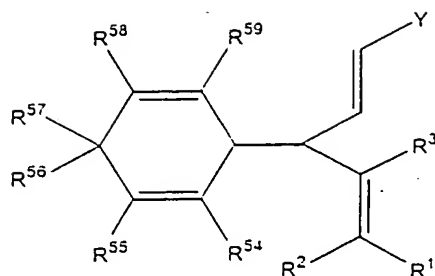


wherein R⁵⁷ is H. The method further includes converting the cyclohexadiene derivative with hydrogenating and oxidizing agents under conditions effective to form the compound.

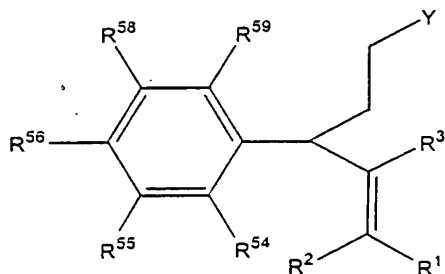
The present invention also relates to a method for preparing a compound having the formula:



R¹, R², and R³ are independently selected from H, an alkyl group, an aryl group, or a vinyl group, or R¹ and R³, together with the atoms to which they are bonded, form a 5-12 membered ring; R⁵⁴, R⁵⁵, R⁵⁶, R⁵⁸, and R⁶⁵ are independently selected from the group consisting of H, alkyl groups, aryl groups, halogen, amino groups, alkoxy groups, hydroxy groups, and acid groups; R⁶² represents an alkyl moiety; or R⁶⁵ and R⁶² together represent the atoms necessary to complete a 5-12 membered ring. The method includes providing a cyclohexadiene derivative having the formula:



where R⁵⁷ is H, R⁵³ is independently selected from the group consisting of H, alkyl groups, aryl groups, halogens, amino groups, alkoxy groups, hydroxy groups, and acid groups, and Y is an electron withdrawing group. The cyclohexadiene derivative is then converted with hydrogenating and oxidizing agents under conditions effective to form a phenyl derivative having the formula:



and the phenyl derivative is converted under conditions effective to produce the compound.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, "alkyl" is meant to include linear alkyls, branched alkyls, and cycloalkyls, each of which can be substituted or unsubstituted. "Alkyl" is also meant to include lower linear alkyls (e.g., C1-C6 linear alkyls), such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, and n-hexyl; lower branched alkyls (e.g., C3-C8 branched alkyls), such as isopropyl, t-butyl, 1-methylpropyl, 2-methylpropyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,2-dimethylpropyl, 1,1-

dimethylpropyl, 2,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 2-methyl-2-ethylpropyl, 2-methyl-1-ethylpropyl, and the like; and lower cycloalkyls (e.g., C3-C8 cycloalkyls), such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

"Alkyl", as use herein, is meant to include unsubstituted alkyls, such as those set forth above, in which no atoms other than carbon and hydrogen are present. "Alkyl", as use herein, is also meant to include substituted alkyls. Suitable substituents include aryl groups (which may themselves be substituted), heterocyclic rings (saturated or unsaturated and optionally substituted), hydroxy groups, alkoxy groups (which is meant to include aryloxy groups (e.g., phenoxy groups)), thiol groups, alkylthio groups, arylthio groups, amine groups (unsubstituted, monosubstituted, or disubstituted, e.g., with aryl or alkyl groups), carboxylic acid groups, carboxylic acid derivatives (e.g., carboxylic acid esters, amides, etc.), phosphine groups, sulfonic acid groups, halogen atoms (e.g., Cl, Br, and I), and the like. Further, alkyl groups bearing one or more alkenyl or alkynyl substituents (e.g., a methyl group itself substituted with a prop-1-en-1-yl group to produce a but-2-en-1-yl substituent) is meant to be included in the meaning of "alkyl".

As used herein, "alkylene" refers to a bivalent alkyl group, where alkyl has the meaning given above. Linear, branched, and cyclic alkylenes, as well as examples thereof, are defined in similar fashion with reference to their corresponding alkyl group. Examples

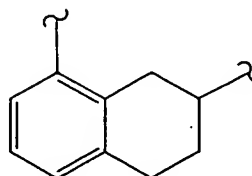
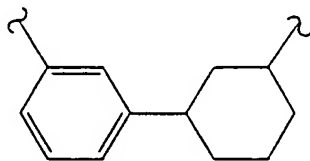
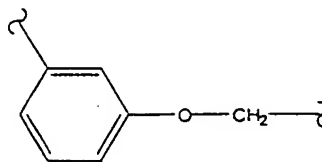
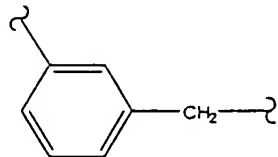
of alkylenes include eth-1,1-diyl (i.e., $-\text{CH}(\text{CH}_3)-$), eth-1,2-diyl (i.e., $-\text{CH}_2\text{CH}_2-$), prop-1,1-diyl (i.e., $-\text{CH}(\text{CH}_2\text{CH}_3)-$), prop-1,2-diyl (i.e., $-\text{CH}_2-\text{CH}(\text{CH}_3)-$), prop-1,3-diyl (i.e., $-\text{CH}_2\text{CH}_2\text{CH}_2-$), prop-2,2-diyl (e.g. $-\text{C}(\text{CH}_3)_2-$), cycloprop-1,1-diyl, cycloprop-1,2-diyl, cyclopent-1,1-diyl, cyclopent-1,2-diyl, cyclopent-1,3-diyl, cyclohex-1,1-diyl, cyclohex-1,2-diyl, cyclohex-1,3-diyl, cyclohex-1,4-diyl, but-2-en-1,1-diyl, cyclohex-1,3-diyl, but-2-en-1,4-diyl, but-2-en-1,2-diyl, but-2-en-1,3-diyl, but-2-en-2,3-diyl. Also included in the meaning of the term "alkylene" are compounds having the formula $-\text{R}'-\text{R}''-$, where $-\text{R}'$ represents a linear or branched alkyl group and R'' represents a cycloalkyl group, such as moieties having the formula:



As used herein, "aryl" is meant to include aromatic rings, preferably having from 4 to 12 members, such as phenyl rings. These aromatic rings can optionally contain one or more heteroatoms (e.g., one or more of N, O, and S), and, thus, "aryl", as used herein, is meant to include heteroaryl moieties, such as pyridyl rings and furanyl rings. The aromatic rings can be optionally substituted. "Aryl" is also meant to include aromatic rings to which are fused one or more other aryl rings or non-aryl rings. For example, naphthyl groups, benzimidazole groups, and 5,6,7,8-tetrahydro-2-naphthyl groups (each of which can be optionally substituted) are aryl groups for the purposes of the present application. As indicated above, the aryl rings can be optionally substituted. Suitable substituents include alkyl groups

(which can optionally be substituted), other aryl groups (which may themselves be substituted), heterocyclic rings (saturated or unsaturated), hydroxy groups, alkoxy groups (which is meant to include aryloxy groups (e.g., phenoxy groups)), thiol groups, alkylthio groups, arylthio groups, amine groups (unsubstituted, monosubstituted, or disubstituted, e.g., with aryl or alkyl groups), carboxylic acid groups, carboxylic acid derivatives (e.g., carboxylic acid esters, amides, etc.), phosphine groups, sulfonic acid groups, halogen atoms (e.g., Cl, Br, and I), and the like.

As used herein, "arylene" is meant to include a bivalent aryl group in which both valencies are present on aromatic carbons. Examples of such groups include, for example, 1,3-phenylene, 1,4-phenylene, 5-methyl-1,3-phenylene, pyrid-2,3-diyl, pyrid-2,4-diyl, pyrid-2,5-diyl, pyrid-3,5-diyl, 1,3-naphthylene, 1,7-naphthylene, 1,8-naphthylene, 5,6,7,8-tetrahydro-1,3-naphthylene. "Arylene", as used herein, is also meant to include a bivalent group having the formula $-R-R'-$, where R is an alkyl group and R' is an aryl group. As the structure of $-R-R'-$ indicates, one of the valencies is on the R (i.e., alkyl) portion of the $-R-R'-$ moiety and the other of the valencies resides on the R' (i.e., aryl) portion of the $-R-R'-$ moiety. Examples of this type of arylene moiety include moieties having the formulae:



and the like.

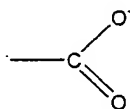
As used herein, "alkoxy" is meant to include groups having the formula $-O-R$, where R is an alkyl or aryl group. They include methoxy, ethoxy, propoxy,
5 phenoxy, 4-methylphenoxy, and the like.

As used herein, "electron withdrawing group" refers to those groups which are able to withdraw electron density from adjacent positions in a molecule, as determined, for example, by reference to the tables in
10 the classical works which establish the classification of various substituents according to their electron withdrawing character. For example, reference may be made to the classification established by the Hammett scale, such as the one set forth in Gordon et al., The
15 Chemist's Companion, New York: John Wiley & Sons, pp. 145-147 (1972), which is hereby incorporated by reference. Suitable electron-withdrawing groups include those having a para σ value higher than or equal to about 0.2 or higher than or equal to about 0.3, with reference
20 to the Hammett scale. Particular examples of electron withdrawing groups are moieties having the formulae $-C(O)R$, $-SO_2R$, and $-P(O)RR'$, where R and R' are independently selected from an alkyl group, an aryl group, and an alkoxy group.

25 As used herein, "ring" refers to a homocyclic or heterocyclic ring which can be saturated or unsaturated. The ring can be unsubstituted, or it can be substituted with one or more substituents. The substituents can be saturated or unsaturated, aromatic or
30 nonaromatic, and examples of suitable substituents include those recited above in the discussion relating to substituents on alkyl and aryl groups. Furthermore, two or more ring substituents can combine to form another

ring, so that "ring", as used herein, is meant to include fused ring systems. In the case where the ring is saturated (i.e., in the case where each of the atoms making up the ring are joined by single bonds to other members of the ring), the ring may optionally include
 5 unsaturated (aromatic or nonaromatic) or saturated substituents.

The present invention relates to a compound which includes a first metal atom and second metal atom
 10 that are bonded to one another along an axis. This can be represented by the formula M^1-M^2 , where M^1 and M^2 represent the first and second metal atoms, respectively, and the dash represents the bond and the bond axis. The compound also includes two carboxylate ligands. As used
 15 herein, "carboxylate ligands" means ligands which contain one or more carboxylate groups. As used herein, carboxylate groups mean groups having the formula:



which can be written with the following formula:

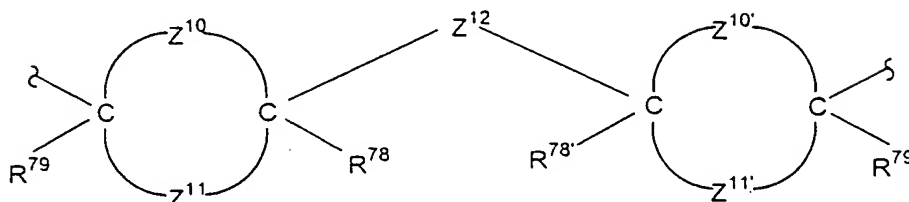


where the dashed line represents the delocalized electron. Alternatively, the carboxylate group can be expressed without showing the delocalized electron, as in the following formula:



In the present invention, each of the two carboxylate ligands includes two carboxylate groups, and

these two carboxylate groups are bonded to each other via a moiety having the formula ("Formula I"):



In Formula I, Z^{10} and Z^{11} , together with the atoms to which they are bonded form a 3-12 membered ring, and $Z^{10'}$ and $Z^{11'}$, together with the atoms to which they are bonded form a 3-12 membered ring. Preferably, Z^{10} and $Z^{10'}$ are the same, and each contains a heteroatom, such as a nitrogen, oxygen, or sulfur. More preferably, Z^{10} and $Z^{10'}$ are the same, and each represents a single heteroatom selected from the group consisting a sulfur atom, an oxygen atom, and an optionally substituted nitrogen atom. Preferably, at least one of Z^{10} and $Z^{10'}$ has the formula -NQ-, at least one of Z^{11} and $Z^{11'}$ is an arylene or alkylene group, and Q is an electron withdrawing group. Still more preferably, both of Z^{10} and $Z^{10'}$ has the formula -NQ-, both of Z^{11} and $Z^{11'}$ is an alkylene group, and Q is an electron withdrawing group. Although one of Z^{10} and Z^{11} and/or one of $Z^{10'}$ and $Z^{11'}$ can represent a direct bond between the carbons to which they are attached, it is preferred that this not be the case and that none of Z^{10} , Z^{11} , $Z^{10'}$, and $Z^{11'}$ represents such a direct bond. R^{78} , $R^{78'}$, R^{79} , and $R^{79'}$ are independently selected from the group consisting of H, an alkyl group, and an aryl group. Preferably, each of R^{78} , $R^{78'}$, R^{79} , and $R^{79'}$ represents a hydrogen. Z^{12} represents an alkylene or arylene group, preferably a substituted or unsubstituted 1,3-phenylene group.

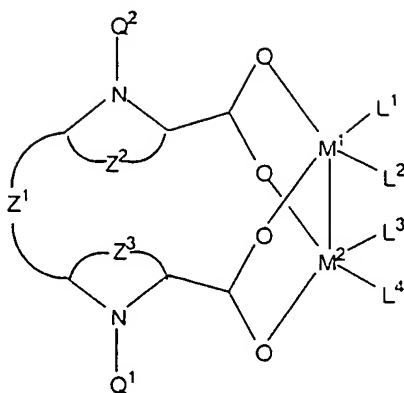
As indicated in the formulae above, each of the two carboxylate groups includes a first carboxylate

oxygen atom ("O¹"), a second carboxylate oxygen atom ("O²"), and a carbon ("C") to which the O¹ and the O² are bonded thereby forming two O¹-C-O² moieties. In the compounds of the present invention, each O¹-C-O² moiety
5 lies in and defines a plane which is substantially parallel to the M¹-M² bond axis. O¹ of each of the two carboxylate groups of each of the two carboxylate ligands is bonded to the first metal atom M¹; O² of each of the two carboxylate groups of each of the two carboxylate
10 ligands is bonded to the second metal atom M². As used in this context, planes which are "substantially parallel" to the M¹-M² bond axis include those planes which do not intersect the M¹-M² bond axis or which intersect the M¹-M² bond axis at an angle of less than
15 20°, preferably less than 10°.

Each of the two carboxylate ligands further comprises at least two chiral centers. These centers, for example, can be included in one or more of Z¹⁰, Z¹¹, Z^{10'}, and Z^{11'}, and/or they can be located at the carbon
20 atoms to which Z¹⁰, Z¹¹, Z^{10'}, and Z^{11'} are bonded. The stereochemistry at these chiral moieties are selected such that the compound, taken as a whole, has D₂ symmetry. Molecules having D₂ symmetry are molecules which have a vertical C₂ axis and a set of two C₂ axes
25 perpendicular to the vertical C₂ axis. D₂ symmetry is further described in, for example, Cotton et al., Advanced Inorganic Chemistry, 4th ed., New York: John Wiley & Sons, pages 28-46 (1980), which is hereby incorporated by reference.

30 Illustrative examples of such compounds and methods of making and using them are described below.

The present invention, in another embodiment thereof, relates to compounds having the formula ("Formula II"):



M¹ and M² are the same or different and are transition metal atoms or ions, examples of which include Sc, Y, the Lanthanides, the Actinides, Ti, Zr, Hf, V, Nb, Ta, Cr, Mo, W, Mn, Tc, Re, Fe, Ru, Os, Co, Rh, Ir, Ni, Pd, Pt, Cu, Ag, Au, Zn, Cd, and Hg metal atoms and ions. Preferably, M¹ and M² are the same or different and are selected from the group consisting of zero-valent Rh, zero-valent Ru, zero-valent Mo, zero-valent Pd, and zero-valent Re. More preferably, each of M¹ and M² are Rh.

Z² and Z³, independently, are the atoms necessary to complete a 3-12 membered heterocyclic ring. Examples of such atoms include, for example: substituted or, preferably, unsubstituted alkylene moieties, such as those having the formula $-(CH_2)_i-$, where i is an integer from 1 to 8; and moieties having the formula $-(CH_2)_i-X-(CH_2)_j-$, where i and j each independently represent integers from 0 to 4 and X is a heteroatom, such as O, S, and NR⁷⁰, where R⁷⁰ is a substituted or unsubstituted alkyl, aryl, or heteroaryl group. Preferably, Z² and Z³ are the same, and, more preferably, each of Z² and Z³ have the formula $-CH_2CH_2-$.

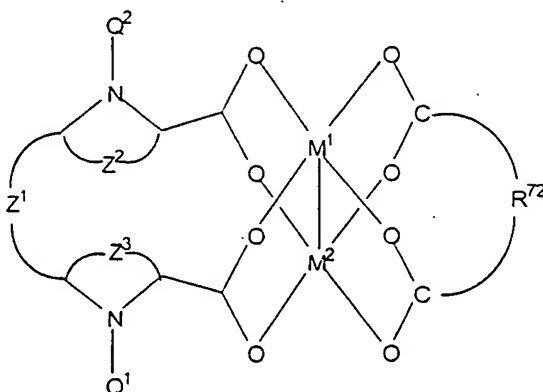
Z¹ is an alkylene or arylene group. Illustratively, Z¹ can have the formula $-(CH_2)_i-$, where i is an integer from 1 to 8. Alternatively, Z¹ can have the formula $-(CH_2)_i-X-(CH_2)_j-$, where i and j each

independently represent integers from 0 to 4 and X is a heteroatom, such as O, S, and NR⁷⁰, where R⁷⁰ is an alkyl or aryl group. Still alternatively, Z¹ can be a cycloalkyl moiety, such as cyclopent-1,3-diyl and
5 cyclohex-1,3-diyl, which can be substituted or unsubstituted. Still alternatively, Z¹ can be an arylene moiety, such as a 1,3-phenylene or 1,3-naphthylene, or an heterocyclic moiety, such as a pyrid-3,5-diyl, pyrid-2,6-diyl, 2H-pyran-3,5-diyl, and tetrahydropyran-3,5-diyl
10 moiety. Preferably, Z¹ is a 1,3-phenylene moiety.

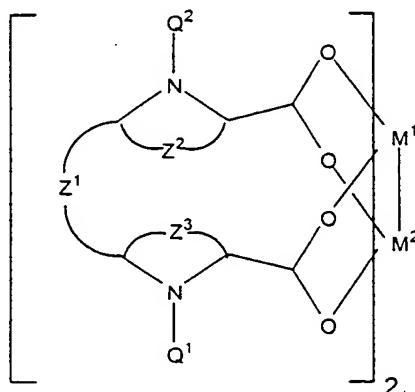
Q¹ and Q² are the same or different and are electron withdrawing groups. Examples of Q¹, suitable for use in the practice of the present invention are moieties having the formulae -C(O)R¹, -SO₂R¹, and
15 -P(O)R¹R^{1'}, and examples of suitable Q² include moieties having the formulae -C(O)R², -SO₂R², and -P(O)R²R^{2'}. In these formulae, each of R¹, R^{1'}, R², and R^{2'} is independently selected from an alkyl group, an aryl group, and an alkoxy group. Preferably, Q¹ has the
20 formula -SO₂R¹; Q² has the formula -SO₂R²; and R¹ and R² are the same or different and are substituted or unsubstituted alkyl or aryl groups. More preferably, Q¹ has the formula -SO₂R¹; Q² has the formula -SO₂R²; and each of R¹ and R² is independently selected from the group
25 consisting of 4-(t-butyl)phenyl, 2,4,6-trimethylphenyl, and 2,4,6-triisopropylphenyl.

In the above Formula II, L¹ and L³, taken together, represent a -O-CR¹³-O- moiety, and L² and L⁴, taken together, represent a -O-CR¹⁴-O- moiety. In these
30 moieties, R¹³ and R¹⁴ can be the same or they can be different, and each is independently selected from the group consisting of alkyl groups and aryl groups. Alternatively, R¹³ and R¹⁴ can represent alkylene or arylene groups that are directly or indirectly bonded to

one another. In the latter case, the compound of the present invention can be expressed as the following formula ("Formula III"):



5 where R^{72} represents an alkylene or arylene group. Preferably, R^{13} and R^{14} , taken together, represent an alkylene or arylene group such that the compound of the present invention has the following formula ("Formula IV"):

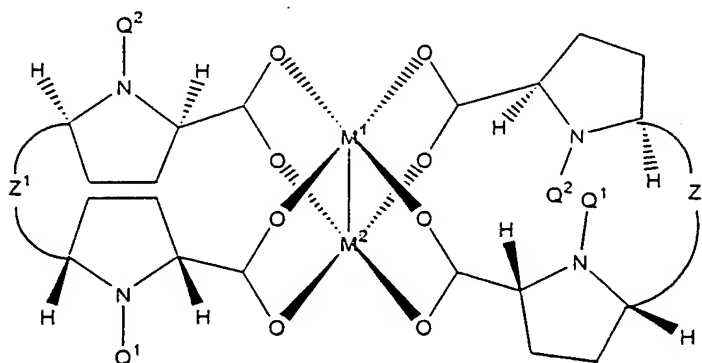


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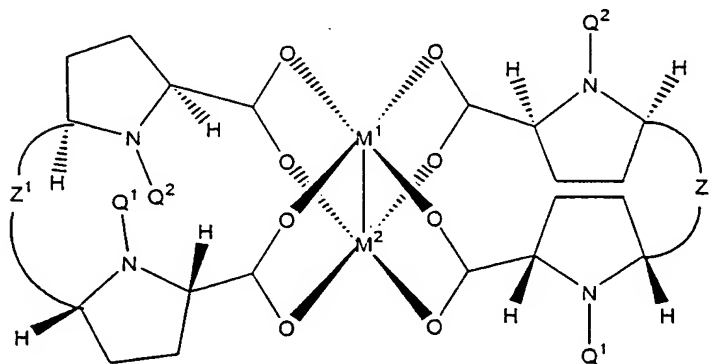
The above-described compounds have at least four chiral centers (i.e., at least the two carbons to which Z^2 is bonded and at least the two carbons to which Z^3 is bonded are chiral). The present invention is not
 15 meant to be limited to any particular set of configurations at the compound's chiral centers, and the structures given above are meant to be broadly read to include any and all possible collections of chiralities.

Each of the compounds having Formulae V and VI can be present alone (i.e., as a pure diastereoisomer) or they can be present in a mixture with one or more different diastereoisomers. Preferably, the compound is substantially free of other diastereoisomers. In this context, "substantially free of other diastereoisomers" means that the molar ratio of other diastereoisomers to the compound is less than 40%, preferably less than 30%, more preferably less than 20%, still more preferably less than 10%, still more preferably less than 5%, still more preferably less than 2%, and still more preferably less than 1%.

Preferred examples of compounds having Formula V and VI, respectively, are those having the formula ("Formula VII"):

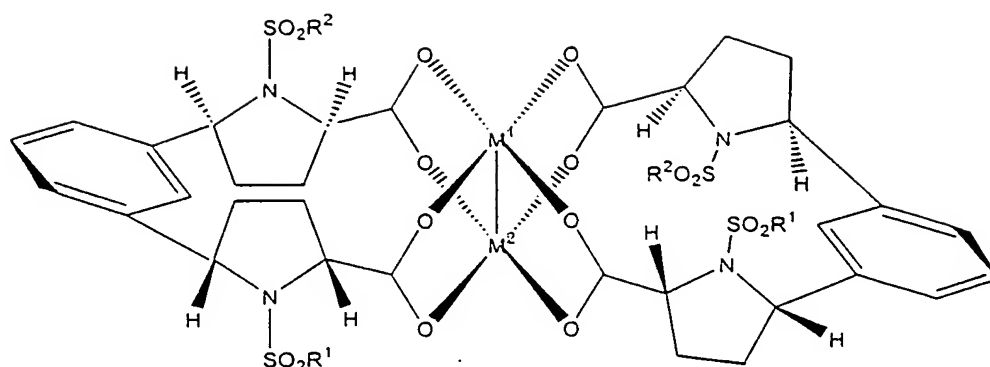


5 and those having the formula ("Formula VIII"):

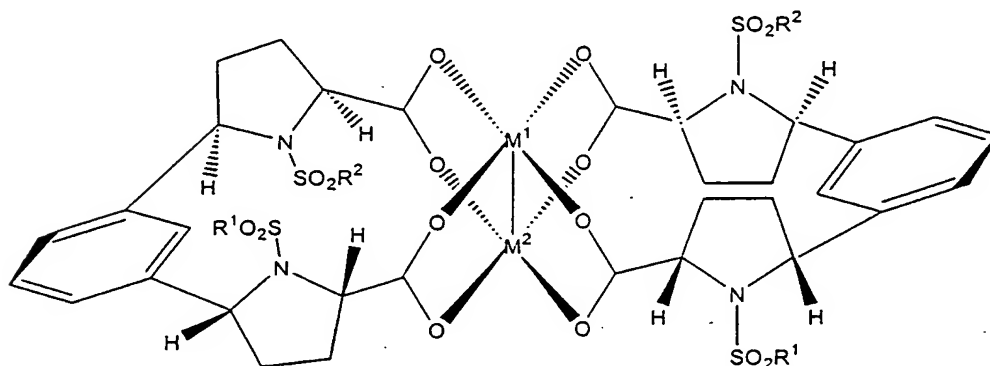


More preferred examples of compounds having Formula V and VI, respectively, are those having the formula ("Formula IX"):

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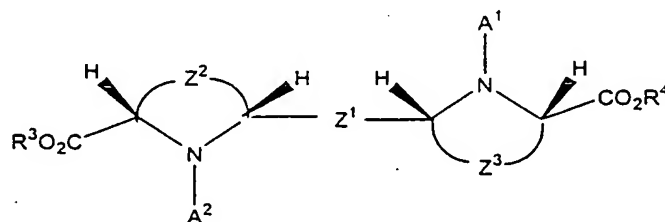
and those having the formula ("Formula X"):



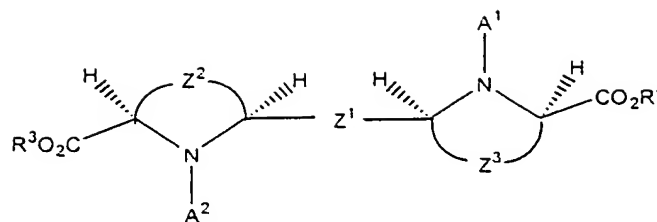
In Formula IX and Formula X, R^1 and R^2 are the same or different and are alkyl or aryl groups.

Compounds of the present invention can be made by a variety of methods. One particularly suitable method, which is the subject of another aspect of the present invention, is illustrated below.

Compounds having Formula II can be prepared from ligands having the formula ("Formula XI"):



from ligands having the formula ("Formula XII"):



or from combinations of these ligands. In each of these formulae, R^3 and R^4 is independently selected from the group consisting of hydrogen, an alkyl group, or an aryl group, and each of A^1 and A^2 is independently selected from the group consisting of a hydrogen atom and an electron withdrawing group. Preferred ligands are those in which R^3 and R^4 are both hydrogen atoms. However, ligands containing other groups in the R^3 and R^4 positions can be employed, for example, by replacing these groups with hydrogen atoms using, for example, conventional ester hydrolysis methods, such as room temperature saponification with a strong base (e.g., lithium hydroxide). Preferred ligands are those in which A^1 and A^2 are both electron withdrawing groups, such as $-C(O)R^2$, $-SO_2R^2$, or $-P(O)R^2R^{2'}$ groups where each of R^1 , $R^{1'}$, R^2 , and $R^{2'}$ is, independently, an alkyl group, an aryl group, or an alkoxy group. However, ligands in which one or both A^1 and A^2 are hydrogen atoms can be used, for example, by replacing the hydrogen atoms with electron withdrawing groups using, for example, conventional acylation, sulfonation, or phosphorylation procedures.

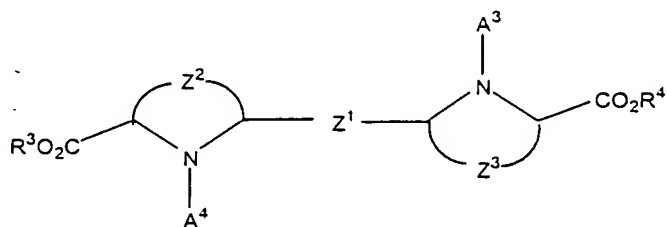
The ligands are converted to the compound of Formula II using a bis-metal salt under conditions effective to produce the compound of Formula II. Suitable bis-metal salts are those having the formula $M^1M^2(OOCR^5)_4$ in which R^5 is an alkyl group or an aryl group and in which M^1 and M^2 are as defined above. Preferably, M^1 and M^2 are the same, and each of the R^5 groups is a C1-C6 alkyl. More preferably, each of M^1 and M^2 is Rh, and

each of the OOCR^5 groups represents an acetate group, in which case the bis-metal salt has the formula $\text{Rh}_2(\text{OOCCH}_3)_4$.

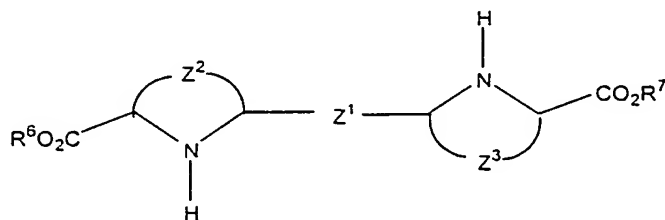
The aforementioned conversion can be advantageously carried out by contacting the bis-metal salt with the ligand for a period of time and at a temperature effective to produce the compound of Formula II. This can be done, for example by pre-forming the bis-metal salt and then contacting the preformed bis-metal salt with the ligand. Alternatively, the bis-metal salt can be produced *in situ*, for example, from an appropriate metal salt. This latter method is particularly advantageous in the case where M^1 and M^2 are the same. For example, in the case where both M^1 and M^2 are Rh, the method can be carried out by mixing the ligand with rhodium diacetate rather than with the preformed dirhodium tetraacetate. Irrespective of whether the bis-metal salt is preformed or permitted to form *in situ*, the reaction is typically carried out in an suitable solvent (e.g., an aromatic solvent, such as benzene, toluene, xylenes, or, preferably, a chlorinated benzene, such as chlorobenzene or dichlorobenzene, or a hydrocarbon solvent, such as hexanes, heptane, iso-octane, or n-octane), with stirring, under reflux, and/or with some other type or agitation, for from about 2 hours to about 10 days, preferably from about 1 day to about 5 days, and at a temperature of from about 30 °C to about 150 °C, preferably from about 120 °C to about 140 °C. Preferably, the reaction solvent is chosen so as to permit the reaction to be carried out at a reflux temperature of from about 120 °C to about 140 °C. Furthermore, preferably, the reaction is carried out in the presence of a compound capable of neutralizing acids. Where the reaction is carried out under reflux, this can

be advantageously achieved by refluxing the solvent through a soxhlet extraction apparatus containing calcium carbonate or another acid-neutralizing compound. The resulting product can be separated from the reaction mixture by conventional means (e.g., by precipitation and filtering and/or by removing the solvent, preferably under vacuum), and it can be optionally purified, for example, by crystallization or chromatography.

The ligands used in the above procedure can be produced using a number of methods. Illustratively, N-substituted ligands having the formula ("Formula XIII"):



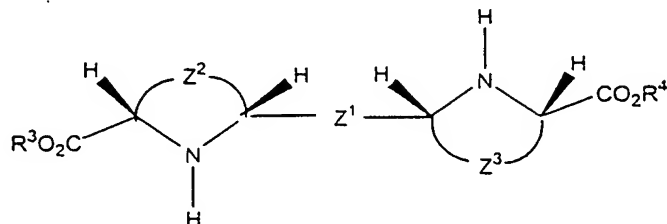
in which A³ and A⁴ are independently selected from the group consisting of -C(O)R², -SO₂R², and -P(O)R²R^{2'} and in which Z¹, Z², Z³, R¹, R^{1'}, R², R^{2'}, R³, and R⁴ are defined as they were above in the discussion relating to Formulae XI and XII, can be produced by the following method. The method includes providing an N-unsubstituted compound having the formula ("Formula XIV"):



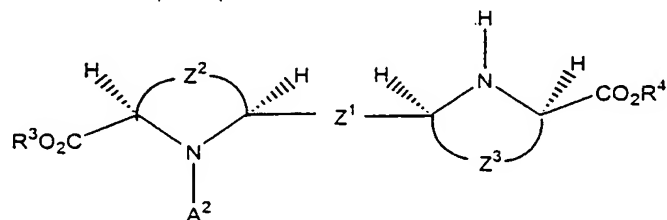
wherein each of R⁶ and R⁷ is independently selected from an alkyl group or an aryl group, and converting the N-unsubstituted compound to the N-substituted compound with an acylating agent, a sulfonylating agent, or a phosphorylating agent. Examples of suitable sulfonylating agents include arylsulfonyl chlorides, such as

benzenesulfonyl chloride, 4-methylbenzenesulfonyl chloride, and 2,4,6-triisopropylbenzenesulfonyl chloride. Typically this conversion is carried out by contacting at least two equivalents, preferably from about 2.3 to about 5 4 equivalents, of acylating agent, sulfonylating agent, or phosphonylating agent with the N-unsubstituted compound at a temperature of from about 10 °C to 100 °C, preferably at about room temperature, for from about 15 minutes to about 10 days, preferably for from about 3 10 hours to about 5 days. The reaction can be carried out neat (i.e., without the use of solvent), or it can be carried out in a suitable inert solvent, such an aromatic solvent (e.g., benzene and toluene), an alkane solvent (e.g., hexanes), a chlorinated solvent (e.g., 15 chlorobenzene or chloroform), or a ketone solvent (e.g., acetone). In some cases, the reaction can be quite vigorous and may benefit from slow addition (e.g., dropwise addition) of the acylating agent, sulfonylating agent, or phosphonylating agent to the N-unsubstituted 20 compound while cooling the reaction mixture, with for example, an ice-water bath. Typically, these reactions produce strong acid, which is advantageously neutralized. Neutralization can be carried out by carrying out the reaction in the presence of, for example, an alkali metal 25 carbonate or bicarbonate and/or by washing the reaction mixture with, for example, alkali metal carbonate or bicarbonate. The N-substituted compound can be separated from the reaction mixture by, for example, extraction, precipitation, and/or filtration, and the N-substituted 30 compound, thus separated, can be purified by standard methods, such as recrystallization or chromatography. The method discussed above above for the preparation of compounds having Formula XIII can be readily adapted to prepare substantially diastereomerically pure compounds

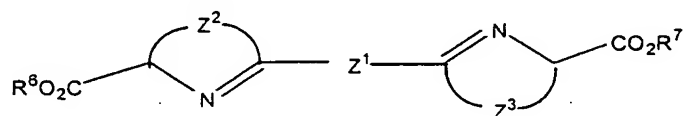
having Formula XI and Formula XII by using, respectively, N-unsubstituted compounds having the formula ("Formula XV") :



5 and having the formula ("Formula XVI") :

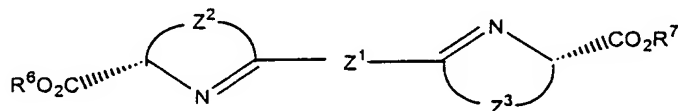


N-unsubstituted compounds having Formula XIV can be advantageously prepared by the following method, to which the present invention also relates. The method includes providing an unsaturated heterocyclic compound
10 having the formula ("Formula XVII") :

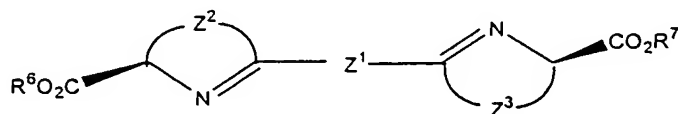


and converting the unsaturated heterocyclic compound to the N-unsubstituted compound using hydrogenation.
15 Typically, the hydrogenation reaction is carried out by contacting the unsaturated heterocyclic compound with a hydrogenating agent, such as hydrogen gas, in the presence of a hydrogenation catalyst, for a suitable length of time (e.g., from about 30 minutes to about 48
20 hours), at a suitable temperature (e.g. from about 10 °C to about 100 °C, preferably at about room temperature), at a suitable pressure (e.g., from about atmospheric pressure to about 100 psi), and in a suitable solvent

(e.g., ether solvents, such as tetrahydrofuran or diethyl ether; alkane solvents, such as hexanes; aromatic solvents, such as benzene or toluene; and alcohol solvents, such as ethanol or isopropanol). It has been found that platinum oxide (e.g., PtO₂) is a particularly effective catalyst for this reaction, although other hydrogenation catalysts, such as those described in Larock in Comprehensive Organic Transformations, New York: Wiley-VCH (1999) ("Larock"), particularly at pp. 7-12, which is hereby incorporated by reference, can be used. Following the reaction, the N-unsubstituted compound is typically separated from catalyst by filtration, and the solvent is then removed, for example, under reduced pressure. Further purification of the resulting N-unsubstituted compound can be carried out by, for example, recrystallization or chromatography. Using the methods set forth above, N-unsubstituted compounds having Formula XV and Formula XVI can be prepared, respectively, from unsaturated heterocyclic compounds having the formula ("Formula XVIII"):



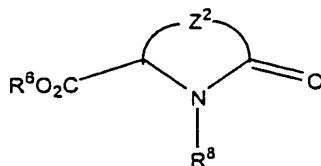
and having the formula ("Formula XIX"):



where Z¹, Z², Z³, R³, R⁴, R⁶, and R⁷ have the meanings set forth above. Preferred unsaturated heterocyclic compounds are those in which Z¹ is a 1,3-phenylene group.

In some situations, it is particularly desirable to convert the ester groups (represented by COOR⁶ and COOR⁷) to the corresponding acid groups (represented by COOR³ and COOR⁴) prior to converting the N-unsubstituted compound to the N-substituted compound. As indicated above, this can be done by conventional deesterification methods, such as for example, saponification. Such saponification can advantageously be carried out on the crude N-unsubstituted compound resulting from the above-described hydrogenation procedure. One suitable saponification method is to reflux the N-unsubstituted compound with an excess of strong alkali metal base in water or a water/solvent mixture. For example, the N-unsubstituted compound can be dissolved and/or suspended in a mixture of tetrahydrofuran, ethanol, and water containing from about a 5 to about a 100 molar excess of lithium hydroxide, and the resulting mixture can be stirred at room temperature or heated, preferably at reflux, for from about 2 hours to about 72 hours. The progress of this reaction can be monitored, for example, by thin layer chromatography to determine when saponification has reached the desired level of completion.

Unsaturated heterocyclic compounds having Formula XVII can be advantageously prepared using the following method, to which the present invention also pertains. In this method, a cyclic ketone having the formula ("Formula XX"):



where R⁸ is an amine-protecting group, is converted to the N-unsaturated heterocyclic compound with a bis-

lithium compound having the formula Z^1Li_2 . For example, in the case where Z^1 is a 1,3-phenylene moiety, the bis-lithium compound used in this reaction is 1,3-dilithiobenzene.

5 "Amine protecting group", as used herein refers to any group known in the art of organic synthesis for the protection of amine groups. Suitable amine protecting groups are listed in Greene et al., Protective Groups in Organic Synthesis, New York: John Wiley & Sons
10 (1991), which is hereby incorporated by reference. Examples of amine protecting groups include, but are not limited to, acyl type amine protecting groups, such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; aromatic carbamate type amine protecting groups, such as
15 benzyloxycarbonyl and substituted benzyloxycarbonyls, 1-(p-biphenyl)-1-methylethoxy-carbonyl, and 9-fluorenylmethyloxycarbonyl; aliphatic carbamate type amine protecting groups, such as tert-butyloxycarbonyl ("BOC"), ethoxycarbonyl, diisopropylmethoxycarbonyl, and
20 allyloxycarbonyl; cyclic alkyl carbamate type amine protecting groups, such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; alkyl type amine protecting groups, such as triphenylmethyl (i.e., trityl) and benzyl; trialkylsilane type amine protecting groups, such as
25 trimethylsilane; and thiol containing type amine protecting groups, such as phenylthiocarbonyl and dithiasuccinoyl. BOC is the preferred amine protecting group.

The reaction of the cyclic ketone with the bis-
30 lithium compound is preferably carried out using conventional lithium alkylation procedures. Typically the reaction is carried out in an inert solvent (e.g., tetrahydrofuran or diethyl ether) and in the strict absence of water by slowly adding (e.g., over the course

of from about 30 minutes to about 2 hours) an excess (e.g., from about 2 to about 10 equivalents) of the cyclic ketone (preferably dissolved in inert solvent) to the dilithium compound (preferably also dissolved in the inert solvent) at reduced temperatures (e.g., from about 0 °C to about -78 °C). The resulting mixture is then typically permitted to warm to room temperature, with stirring, and stirring is continued for from about 2 hours to about 4 days, preferably from about 15 hours to about 30 hours. After the reaction is complete, the mixture is typically poured into water and extracted with an organic solvent (e.g., ethyl acetate). The organic solvent is dried (e.g., over MgSO_4) and removed, advantageously under reduced pressure.

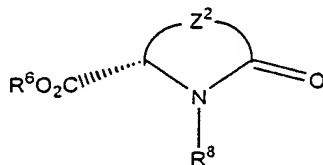
The amine protecting group can then be cleaved using conventional methods, such as, in the case where the amine protecting group is BOC, by treating the reaction product with an excess (e.g., from about 20 to about 100 equivalents, based on the amount of dilithium compound employed) of trifluoroacetic acid ("TFA"). This treatment is typically carried out in a suitable solvent (e.g., a chlorinated hydrocarbon, such as dichloromethane or chloroform) for from about 30 minutes to about 48 hours at from about 10 °C to about 100 °C, preferably at about room temperature. Subsequently, the excess acid is neutralized (e.g., with bicarbonate), the solvent is removed (e.g., under reduced pressure), and the unsaturated heterocyclic compound is optionally further purified (e.g., by recrystallization and/or chromatography).

Many suitable dilithium compounds can be purchased commercially. Alternatively, these compounds can be prepared by conventional methods, such as those set forth in Fossatelli et al., "1,3-Dilithiobenzene and

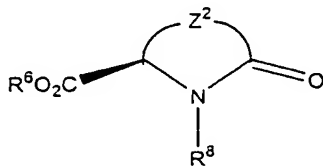
1,4-Dilithiobenzene," Rec. Trav. Chim. Pays-Bas, 113:527-528 (1994), which is hereby incorporated by reference.

Cyclic ketones that can be used to prepare the unsaturated heterocyclic compound, as described above, can be obtained from commercial sources, or, alternatively, they can be produced, for example, using the methods described in, for example, Ezquerra et al., "Stereoselective Reactions of Lithium Enolates Derived From N-BOC Protected Pyroglutamic Esters," Tetrahedron, 49:8665-8678 (1993), which is hereby incorporated by reference.

In the case where the N-unsaturated heterocyclic compound has Formula XVIII, it is advantageous to employ a cyclic ketone having the formula ("Formula XXI"):



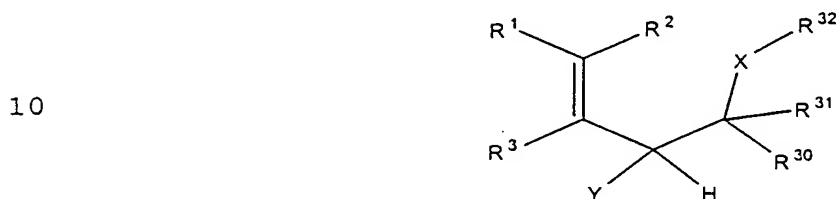
In the case where the N-unsaturated heterocyclic compound has Formula XIX, it is advantageous to employ a cyclic ketone having the formula ("Formula XXII"):



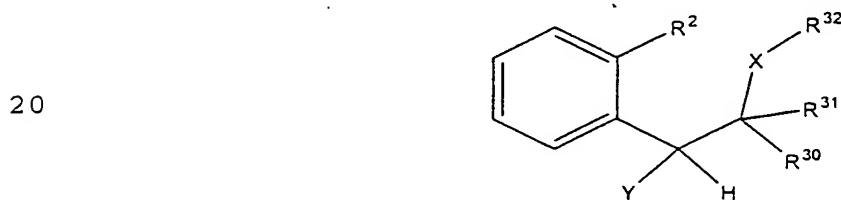
The above compounds (e.g., those represented by Formulae II, III, IV, V, VI, VII, VIII, IX, and X as well as those containing the moiety denoted Formula I) can be used to effect a variety of organic transformations. One such illustrative organic transformation is the C-H insertion reaction, such as those C-H insertion reactions in which bis-transition metal catalysts have been

previously employed, especially in cases where substantially diastereomerically pure products are desired. Several of such C-H insertion reactions are described below. However, nothing herein should be construed as meaning that the reactions described below must be carried out with the compounds described above.

The present invention further relates to a method of producing a compound having the formula ("Formula XXIII"):



R^1 , R^2 , and R^3 are independently selected from H, alkyl, aryl, or vinyl, or R^1 and R^3 , together with the atoms to which they are bonded, form a 5-12 membered ring, such as a cyclohexene ring, or a cyclohexa-1,3-diene ring. The method is particularly well-suited for preparing compounds in which R^1 and R^3 , together with the atoms to which they are bonded, form an aromatic ring, such as a phenyl ring, in which case the compound produced by this method has the formula ("Formula XXIV"):



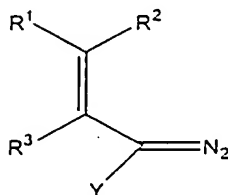
Y is an electron withdrawing group, examples of which include moieties having the formulae: $-C(O)R^{77}$, $-SO_2R^{77}$, and $-P(O)R^{77}R^{77'}$. In these formulae, each of R^{77} and $R^{77'}$ is independently selected from an alkyl group, an aryl group, and an alkoxy group. Preferably, Y has the

formula CO_2R^{12} where R^{12} is an alkyl group or an aryl group.

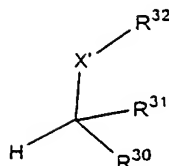
X is CH_2 , O, or NR^{11} , and R^{11} is H, an alkyl group, an aryl group, an acyl group, an alkoxy carbonyl group, or a silyl group having the formula $-\text{SiR}^{33}\text{R}^{34}\text{R}^{35}$, where R^{33} , R^{34} , and R^{35} are independently selected from an alkyl group and an aryl group.

Each of R^{30} and R^{31} is independently selected from the group consisting of H, alkyl, aryl, and vinyl. R^{32} is an alkyl group, an aryl group, an acyl group, an alkoxy carbonyl group, or a silyl group having the formula $-\text{SiR}^{36}\text{R}^{37}\text{R}^{38}$, where R^{36} , R^{37} , and R^{38} are independently selected from an alkyl group and an aryl group. Alternatively, R^{31} and R^{32} , together with the atoms to which they are bonded, can form a 5-12 membered ring, such as a cyclopentyl or cyclohexyl ring (in the case where X is $-\text{CH}_2-$), a piperidinyl ring (in the case where X is N), or a tetrahydrofuranlyl or a tetrahydropyranlyl ring (in the case where X is O). Illustratively, the method of the present invention is well-suited for forming compounds having Formula XXIV in which X is not CH_2 when each of R^{30} and R^{31} is H.

The method includes providing a diazo compound having the formula ("Formula XXV"):



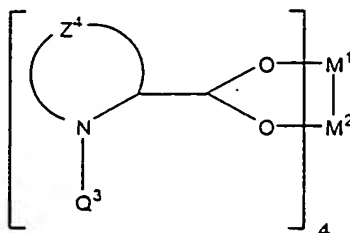
in which R^1 , R^2 , R^3 , and Y have the same meanings as given above with reference to Formula XXIV. The method further includes converting the diazo compound with a compound having the formula ("Formula XXVI"):



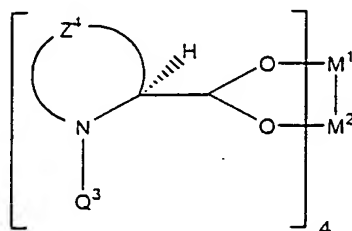
in the presence of a bis-transition metal catalyst and under conditions effective to produce the compound. In compound XXVI, R^{30} , R^{31} , and R^{32} are defined as they are
 5 above with regard to Formula XXIV. When, in the desired product, X is CH_2 or O, X' in Formula XXVI is CH_2 or O, respectively. When, in the desired product, X is NR^{11} , X' in Formula XXII is $NR^{11'}$ and $R^{11'}$ is an alkyl group, an aryl group, an acyl group, an alkoxy carbonyl group, or a
 10 silyl group (e.g., a triarylsilyl group, or a trialkylsilyl group). It is particularly preferred that, when X' represents an $NR^{11'}$ group, $R^{11'}$ represents an alkoxy carbonyl amine protecting group, such as BOC.

Suitable bis-transition metal catalysts for use
 15 in this reaction include, for example, catalysts having the formula L_4M-ML_4 where each of the L's is the same or different and represents a suitable ligand (e.g., an oxygen-from an acetate moiety) and each of the M's is the same or different and represents a transition metal
 20 (e.g., Rh or Ru). Dirhodium and diruthenium catalysts, especially dirhodium or diruthenium tetracarboxylate catalysts, are preferred.

Illustrative dirhodium or diruthenium tetracarboxylate catalysts are those having the formula
 25 ("Formula XXVII"):



In Formula XXVII, each of M^1 and M^2 is Rh or Ru. Z^4 represents the atoms necessary to complete a 3-12 membered heterocyclic ring, such as an alkylene moiety (e.g., a $-\text{CH}_2\text{CH}_2\text{CH}_2-$ moiety). Q^3 is an electron withdrawing group, such as a group having the formulae $-\text{C}(\text{O})\text{R}^9$, $-\text{SO}_2\text{R}^9$, or $-\text{P}(\text{O})\text{R}^9\text{R}^{9'}$, where each of R^9 and $\text{R}^{9'}$ is independently selected from an alkyl group, an aryl group, and an alkoxy group. In cases where the desired product of Formula XXVIII is substantially diastereomerically pure, it is advantageous to use a substantially chirally pure catalyst, such as a dirhodium or diruthenium tetracarboxylate catalyst having the formula ("Formula XXVIII"):



More preferably, the dirhodium or diruthenium tetracarboxylate catalyst having Formula XXVIII has D_2 symmetry.

Specific examples of suitable compounds having Formulae XXVII and XXVIII include: $\text{Rh}_2(\text{DOSP})_4$, which is a compound having Formula XXVII in which each of M^1 and M^2 is Rh, Z^4 is a $-\text{CH}_2\text{CH}_2\text{CH}_2-$ group, and Q^3 represents a 4-dodecylphenylsulfonyl moiety; $\text{Rh}_2(\text{S-DOSP})_4$, which is a compound having Formula XXVIII in which each of M^1 and M^2 is Rh, Z^4 is a $-\text{CH}_2\text{CH}_2\text{CH}_2-$ group, and Q^3 represents a 4-dodecylphenylsulfonyl moiety; $\text{Rh}_2(\text{TBSP})_4$, which is a compound having Formula XXVII in which each of M^1 and M^2 is Rh, Z^4 is a $-\text{CH}_2\text{CH}_2\text{CH}_2-$ group, and Q^3 represents a 4-t-butylphenylsulfonyl moiety; and $\text{Rh}_2(\text{S-TBSP})_4$, which is a compound having Formula XXVIII in which each of M^1 and M^2

is Rh, Z¹ is a -CH₂CH₂CH₂- group, and Q³ represents a 4-t-butylphenylsulfonyl moiety. These and other illustrative compounds having Formulae XXVII and XXVIII are described in greater detail in Davies, "Rhodium-Stabilized Vinylcarbenoid Intermediates in Organic Synthesis," Current Organic Chemistry, 2:463-488 (1998) ("Davies"), which is hereby incorporated by reference.

Particularly suitable bis-transition metal catalysts for carrying out the conversion of XXV with XXVI are those having Formulae II, III, IV, V, VI, VII, VIII, IX, and X, as defined and discussed above, particularly where M¹ and M² are Rh or Ru. Other particularly suitable bis-transition metal catalysts for carrying out the conversion of XXV with XXVI are chiral dirhodium or diruthenium catalysts, especially those which include a first metal atom and a second metal atom that are bonded to one another along an axis and two carboxylate ligands. Each of the two carboxylate ligands includes two carboxylate groups bonded to each other via a moiety having Formula I. Each of the two carboxylate groups includes a first carboxylate oxygen atom ("O¹"), a second carboxylate oxygen atom ("O²"), and a carbon ("C") to which the O¹ and the O² are bonded thereby forming two O¹-C-O² moieties, and each O¹-C-O² moiety defines a plane which is substantially parallel to the axis. O¹ of each of the two carboxylate groups of each of the two carboxylate ligands is bonded to the first metal atom; O² of each of the two carboxylate groups of each of the two carboxylate ligands is bonded to the second metal atom; each of the two carboxylate ligands further comprises at least two chiral centers; and the compound has D₂ symmetry. Such bis-transition metal catalysts are discussed in greater detail above.

Typically, the reaction is carried out by mixing the catalyst with the compound of Formula XXVI. In the case where the compound of Formula XXVI is a liquid (e.g., in the case where the compound of Formula XXVI is tetrahydrofuran, tetrahydropyran, pyrrolidine, piperidine, cyclopentane, cyclohexane, etc.), this can be effected without the use of additional solvent. Alternatively, the mixture can be formed using an inert solvent or a solvent which is significantly less reactive toward the diazo compound of Formula XXV than is the compound of Formula XXVI. As an example, it has been found that when the compound of Formula XXVI is tetrahydrofuran, the catalyst and tetrahydrofuran can be mixed neat (i.e., without the use of additional solvent), or cyclohexane can be used as a reaction medium. The amount of catalyst employed is not critical to the practice of the present invention. Typically, the mole ratio of the catalyst to the compound of Formula XXVI is from about 1:10,000 to about 1:20, preferably from about 1:500 to about 1:50, and more preferably from about 1:200 to about 1:100.

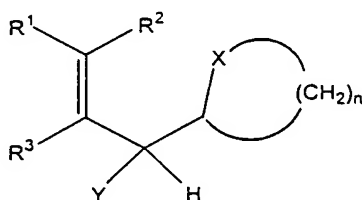
Once the catalyst and compound of Formula XXVI are mixed, the diazo compound of Formula XXV is added, preferably with stirring. Addition can be carried out in a single portion, continuously, or batchwise. Slow, dropwise addition, using, for example, a syringe pump, is frequently advantageous. The amount of diazo compound of Formula XXV added is generally dependent on the amount of the compound of Formula XXVI present in the reaction mixture. Typically the mole ratio of the compound of Formula XXVI to the diazo compound of Formula XXV is from about 1:10 to about 10:1, preferably from about 6:1 to about 1:1, more preferably from about 4:1 to about 2:1. The addition can be carried out at any suitable

temperature from the freezing point to the boiling point of the solvent and/or the compound of Formula XXVI. Typically, the addition is carried out from about -50 °C to about 60 °C. Room temperature addition and addition
5 at about 10 °C have been found to be advantageous. Optimization of reaction conditions, including temperature of addition, is more important when diastereomerically pure product is desired. Generally, formation of diastereomerically pure product is favored
10 by lower addition temperatures (e.g., from about -50 °C to about 10 °C).

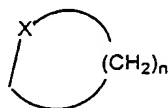
Applicants have unexpectedly discovered that, when the reaction of the present invention is carried out substantially in the absence of oxygen, the resulting
15 product has significantly improved yield when compared to reactions which are not carried out substantially in the absence of oxygen. As used herein, "substantially in the absence of oxygen" means that the liquid reactants and solvents (if any) employed in carrying out the reaction
20 are degassed, for example by bubbling an inert gas (e.g., nitrogen or argon) therethrough, that the reaction is carried out under blanket of inert gas or under vacuum, and that all transfers are carried out such that ambient air is excluded (e.g., by using rubber septums, gas tight
25 syringes, and the like). Illustratively, applicants have unexpectedly discovered that when X is O or CH₂, when R¹ and R³, together with the atoms to which they are bonded, form a 5-12 membered ring, and when R³¹ and R³², together with the atoms to which they are bonded, form a 5-12
30 membered ring, carrying out the reaction substantially in the absence of oxygen produces a product having significantly improved diastereoisomeric purity. When carrying out these reactions substantially in the absence

of oxygen, it is advantageous to use a chiral catalyst, preferably a chiral catalyst having D_2 symmetry.

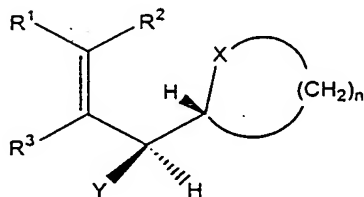
The conversion of the compound of Formula XXV with a compound of Formula XXVI to produce a compound of Formula XXIII described above is particularly suitable
5 for preparing compounds having the formula ("Formula XXIX"):



In this case, the conversion of the diazo compound of
10 Formula XXV is carried out with a cyclic compound having the formula ("Formula XXX"):



in which X' is defined as above and n is 3-10. In this embodiment, R^1 and R^3 , together with the atoms to which
15 they are bonded, preferably form a phenyl ring, and Y preferably has the formula $-CO_2R^{10}$ where R^{10} is an alkyl or aryl group. The method is particularly suitable for making compounds in which X is NR^{11} and in which n is 3 or 4. The method is also particularly suitable for making
20 compounds having the formula ("Formula XXXI"):

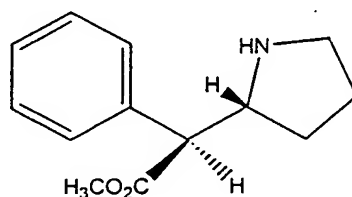


in which case the bis-transition metal catalyst employed is a chiral bis-transition metal catalyst. For example,

by using the *S*-isomer of compounds having Formulae II, III, IV, V, VI, VII, VIII, IX, or X, as defined and discussed above (particularly where M^1 and M^2 are Rh or Ru), compounds of Formula XXXI which are substantially
 5 diasteriomERICALLY pure (e.g., > 80% ee, >90% ee, >95% ee, >98% ee, and/or >99% ee) can be prepared.

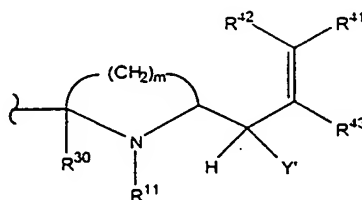
Particularly preferred compounds having Formula XXXI are those in which X is NR^{11} , n is 3, Y is CO_2R^{12} , R^{12} is alkyl or aryl, and R^1 and R^3 , together with the atoms to which
 10 they are bonded, form an aromatic ring. Still more preferred are those compounds of Formula XXXI in which X is NH, R^{12} is a methyl group, and R^1 and R^3 , together with the atoms to which they are bonded, form a phenyl ring. Such compounds have the formula ("Formula XXXII"):

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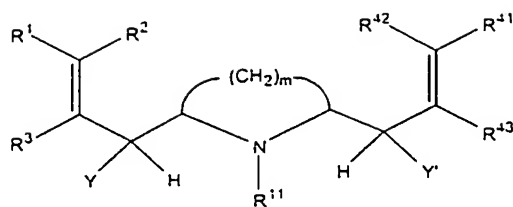


which is also referred to as *threo* methylphenidate and which is believed to be the biologically active form of RITALIN™.

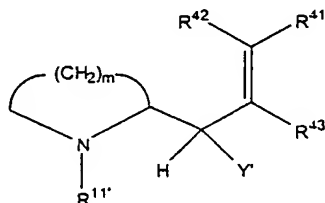
The method of the present invention can also be
 20 used to prepared compounds having Formula XXIII in which X is NR^{11} and in which R^{31} and R^{32} , together with the atoms to which they are bonded represent a ring having the formula ("Formula XXXIII"):



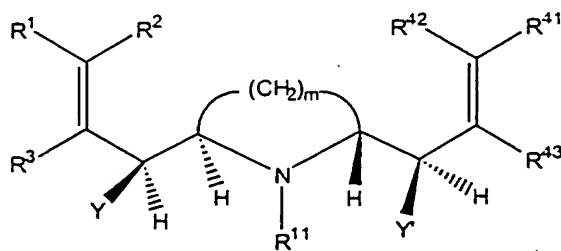
25 where R^{30} is H. That is, the method can be used to prepare compounds having the formula ("Formula XXXIV"):



In these formulae, R^{41} , R^{42} , and R^{43} are independently selected from H, alkyl, aryl, or vinyl, or R^{41} and R^{43} , together with the atoms to which they are bonded, form a 5-12 membered ring. Y' is an electron withdrawing group, for example, the electron withdrawing groups discussed above with regard to Y , and m is 2-9. The reaction involves providing a diazo compound having Formula XXV and converting the diazo compound with a cyclic amine having the formula ("Formula XXXV"):



in the presence of a bis-transition metal catalyst and under conditions effective to produce the compound. Suitable conditions for this reaction are the same as the ones discussed above with regard to the conversion of compounds of Formula XXV with compounds of Formula XXVI. By using a chiral catalyst, compounds having the formula ("Formula XXXVI"):



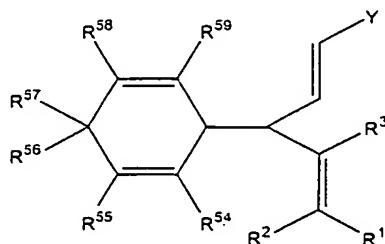
can be produced.

A variety of methods can be used to prepare the cyclic amine having Formula XXXV, but the preferred method is the one described above with regard to preparing compounds having Formula XXIX using diazo compounds of Formula XXV, cyclic compounds of Formula XXX, and a bis-transition metal catalyst. Rather than running the reaction in two steps (i.e., by first reacting a diazo compounds of Formula XXV with a cyclic compound of Formula XXX in which X is N to produce a cyclic amine having Formula XXIX and then reacting the cyclic amine having Formula XXIX with a diazo compound having Formula XXV to produce the desired compound of Formula XXXIV), the reaction can be carried out in a single step by, for example, contacting the cyclic compound of Formula XXX in which X is N with at least two equivalents of a diazo compound of Formula XXV. The reaction conditions suitable for carrying out this one step reaction are the same as those discussed above with regard to the two step method. Preferably, during the first part of the reaction (i.e., during the addition of the first half of the diazo compound having Formula XXV), the reaction is carried out with cooling (e.g., from about -50 °C to about 0 °C). Then the reaction mixture is warmed, and the second part of the reaction (i.e., during the addition of the second half of the diazo compound having Formula XXV) is carried out at elevated temperatures (e.g., from about 20 °C to about 100 °C). Alkanes having melting points of less than about -50 °C and boiling points greater than about 60 °C are the preferred solvents for this reaction.

The compounds prepared by the above method (i.e., compounds having Formulae XXIII, XXIV, XXIX, XXXI, XXXII, XXXIV, and XXXVI) are appropriately functionalized

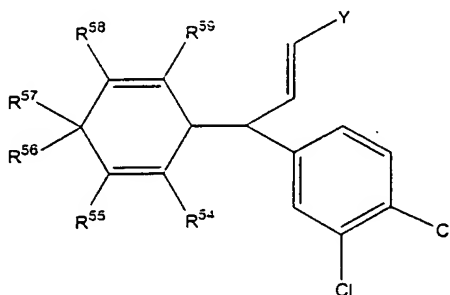
for further conversion by, for example, ester reduction or Grignard addition to highly functionalized bases. In the case where a chiral catalyst is employed, e.g., the *S*-isomer of compounds having Formulae II, III, IV, V, VI, VII, VIII, IX, or X, as defined and discussed above (particularly where M^1 and M^2 are Rh or Ru), these compounds can be used as C_2 symmetric bases, or, as indicated above, they can be further converted (e.g., by ester reduction or Grignard addition) to highly functionalized C_2 bases. C_2 bases are very useful for controlling stereochemistry in organic synthesis, for example, as described in Takahata et al., "New Entry to C_2 Symmetric Trans-2,6-bis(hydroxymethyl)piperidine Derivatives Via the Sharpless Asymmetric Dihydroxylation," Tetrahedron-Asymmetry, 6:1085-1088 (1995) and in Bennani et al., "Trans-1,2-diaminocyclohexane Derivatives as Chiral Reagents, Scaffolds, and Ligands for Catalysis - Applications in Asymmetric Synthesis and Molecular Recognition," Chemical Reviews, 97:3161-3195 (1997), which are hereby incorporated by reference.

The present invention also relates to a method for making a compound having the formula ("Formula XXXVII"):



In Formula XXXVII, R^1 , R^2 , and R^3 are independently selected from H, alkyl, aryl, or vinyl, or R^1 and R^3 , together with the atoms to which they are bonded, form a 5-12 membered ring, such as a cyclohexene ring, or a cyclohexa-1,3-diene ring. The method is

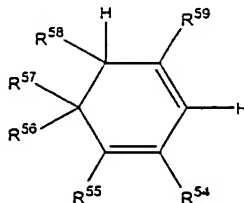
particularly well-suited for preparing compounds in which R^1 and R^3 , together with the atoms to which they are bonded, form an aromatic ring, such as a 3,4-dichlorophenyl ring, in which case the compound produced
5 has the formula ("Formula XXXVIII"):



Y is an electron withdrawing group, examples of which include moieties having the formulae: $-C(O)R^{77}$, $-SO_2R^{77}$, and $-P(O)R^{77}R^{77'}$. In these formulae, each of R^{77}
10 and $R^{77'}$ is independently selected from an alkyl group, an aryl group, and an alkoxy group. Preferably, Y has the formula CO_2R^{12} where R^{12} is an alkyl group or an aryl group.

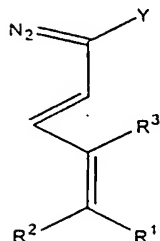
Each of R^{54} , R^{55} , R^{56} , R^{57} , R^{58} , and R^{59} is
15 independently selected from the group consisting of H, alkyl, aryl, halogen, and alkoxy. Preferably, each of R^{54} , R^{55} , R^{56} , R^{57} , R^{58} , and R^{59} is hydrogen.

The method includes providing a 1,3-cyclohexadiene having the formula ("Formula XXXIX"):



where R^{54} , R^{55} , R^{56} , R^{57} , R^{58} , and R^{59} are defined as above.
The method further includes converting the 1,3-

cyclohexadiene with a diazo compound having the formula ("Formula XL"):



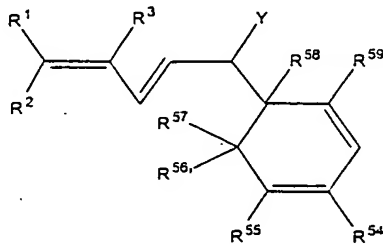
in which Y, R¹, R², and R³ are as defined above. The
5 conversion is carried out in the presence of a bis-
transition metal catalyst and under conditions effective
to produce the compound.

Suitable bis-transition metal catalysts
include, for example, those catalysts set forth above
10 with regard to the method of producing compounds of
Formula XXIII.

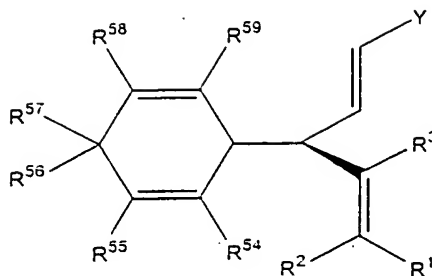
Typically, the reaction is carried out by
mixing the catalyst with the 1,3-cyclohexadiene of
Formula XXXIX. In the case where the 1,3-cyclohexadiene
15 of Formula XXXIX is a liquid (e.g., in the case where the
compound of Formula XXXIX is 1,3-cyclohexadiene), this
can be effected without the use of additional solvent.
Alternatively, the mixture can be formed using an inert
solvent or a solvent which is significantly less reactive
20 towards the diazo compound of Formula XL than is the
compound of Formula XXXIX. Suitable solvents include
alkanes, such as hexanes. The solvent is preferably
dried prior to use using conventional methods, and the
reaction vessel is also preferably dried, such as by
25 flaming or in an oven. The amount of catalyst employed
is not critical to the practice of the present invention.
Typically, the mole ratio of catalyst to compound of
Formula XXXIX is from about 1:10,000 to about 1:20,

preferably from about 1:1000 to about 1:100, and more preferably from about 1:500 to about 1:700.

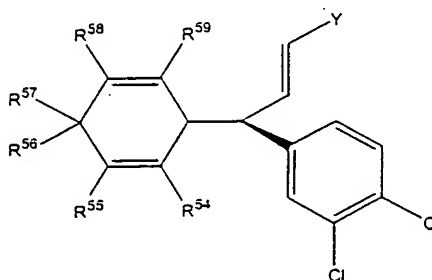
Once the catalyst and compound of Formula XXXIX are mixed, the compound of Formula XL is added, preferably with stirring. Addition can be carried out in a single portion, continuously, or batchwise. Slow, dropwise addition using, for example, a syringe pump is frequently advantageous. The amount of compound of Formula XL added is generally dependent on the amount of compound of Formula XXXIX present in the reaction mixture. Typically the mole ratio of compound of Formula XL to compound of Formula XXXIX is from about 1:10 to about 10:1, preferably from about 1:8 to about 1:1, more preferably from about 1:6 to about 1:4. The addition can be carried out at any suitable temperature from the freezing point to the boiling point of the solvent and/or the compound of Formula XXXIX. Typically, the addition is carried out from about -50 °C to about 60 °C, preferably at about room temperature. Generally, higher temperatures favor an undesirable reverse Cope rearrangement in which compounds having Formula XXXVII rearrange to form compounds having the formula ("Formula XLI"):



The method is also particularly suitable for making compounds having Formula XXXVII which are substantially diasteriomERICALLY pure, such as, for example, compounds having the formula ("Formula XLII"):

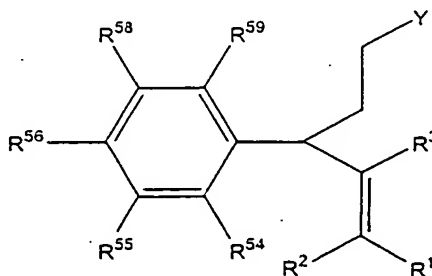


such as compounds having the formula ("Formula XLIII"):



When a substantially diastereomerically selective
 5 reaction is desired, the use of a chiral catalyst,
 preferably one with D_2 symmetry, is preferred. For
 example, by using the *S*-isomer of compounds having
 Formulae II, III, IV, V, VI, VII, VIII, IX, and X, as
 defined and discussed above (particularly where M^1 and M^2
 10 are Rh or Ru), compounds of Formulae XLII and XLIII which
 are substantially diastereomerically pure (e.g., >80% ee,
 >90% ee, >95% ee, >98% ee, and/or >99% ee) can be
 prepared.

The present invention also relates to methods
 15 for making compounds having the formula ("Formula XLIV"):



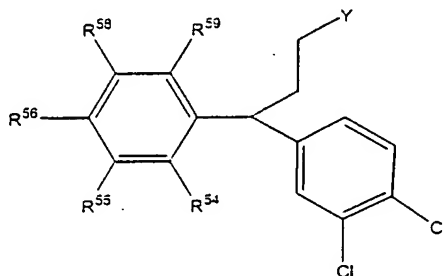
in which R¹, R², R³, R⁵⁴, R⁵⁵, R⁵⁶, R⁵⁹, and Y are defined as they were above for the compounds having Formula XXXVII.

The method includes providing a cyclohexadiene derivative having Formula XXXVII wherein R⁵⁷ is H. Preferred cyclohexadiene derivatives which can be used in this reaction are those described above, and they can be conveniently prepared using, for example, the methods disclosed above. Once the cyclohexadiene derivative is provided, it is converted with hydrogenating and oxidizing agents under conditions effective to form the compound of Formula XLIV. The hydrogenation and oxidation reactions can be carried out simultaneously or sequentially, and, when carried out sequentially, hydrogenation can precede oxidation or oxidation can precede hydrogenation. Suitable hydrogenating agents for use in the present reaction include hydrogen gas in combination with a metal catalyst, such as palladium, preferably palladium on carbon. Other suitable metal catalysts include those set forth in Larock, particularly at pp. 7-12, which is hereby incorporated by reference. Suitable conditions for carrying out such reactions are described, for example, in Larock, particularly at pp. 7-12, and in House, Modern Synthetic Reactions, 2nd ed., Menlo Park, California: The Benjamin/Cummings Publishing Company, pp. 1-34 (1972), which are hereby incorporated by reference.

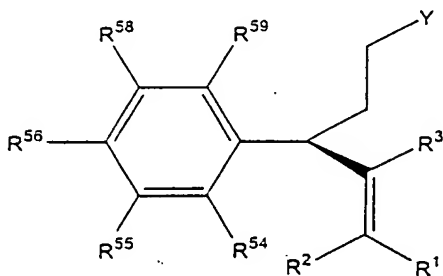
Suitable oxidizing agents for use in the present reaction include those which are generally known to dehydrogenate 1,4-cyclohexadienyl moieties to phenyl moieties, such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone ("DDQ") and tetrachlorobenzoquinone (a.k.a., chloranil). Other suitable oxidizing agents and suitable conditions for carrying out such reactions are

described, for example, in House, Modern Synthetic Reactions, 2nd ed., Menlo Park, California: The Benjamin/Cummings Publishing Company, pp. 34-44 (1972), and in Larock, particularly at p. 189, which are hereby
5 incorporated by reference.

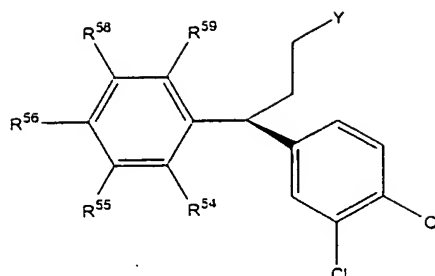
The above-described method is particularly useful for making compounds having Formula XLIV in which Y is an alkoxy carbonyl group (e.g., in which Y has the formula $-COOR^{12}$ and R^{12} is an alkyl group) and/or in which
10 R^1 and R^3 , together with the atoms to which they are bonded, form an aromatic ring, such as a 3,4-dichlorophenyl ring. In the latter case, the compound of Formula XLIV has the formula ("Formula XLV"):



15 Furthermore, by using a cyclohexadiene having Formula XLII (e.g., a cyclohexadiene having Formula XLIII), substantially diastereomerically pure compounds of Formula XLIV, such as those having the formula ("Formula XLVI"):

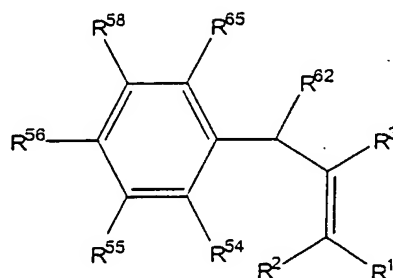


20 and, more particularly, those having the formula ("Formula XLVII"):



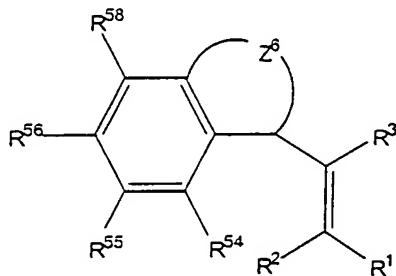
can be prepared.

The present invention, in yet another embodiment thereof, relates to a method for making for
5 preparing a compound having the formula ("Formula XLVIII") :

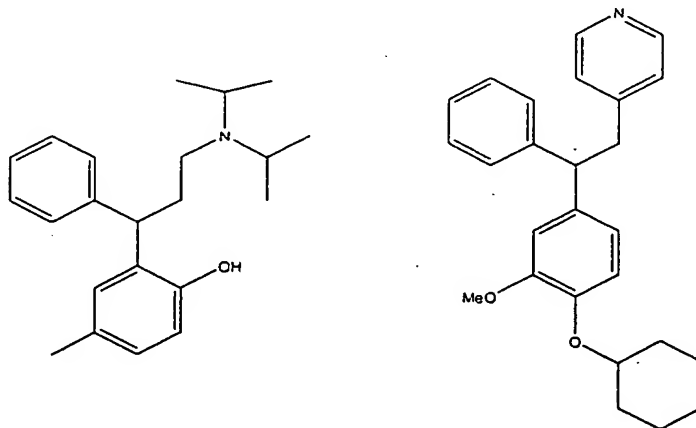


R¹, R², and R³ are independently selected from H, an alkyl
group, an aryl group, or a vinyl group, or R¹ and R³,
10 together with the atoms to which they are bonded, form a
5-12 membered ring. Preferably, R¹ and R³, together with
the atoms to which they are bonded, form an aromatic
ring, such as a substituted or unsubstituted 1,3-
phenylene ring. R⁵⁴, R⁵⁵, R⁵⁶, R⁵⁸, and R⁶⁵ are independently
15 selected from the group consisting of H, alkyl groups,
aryl groups, halogen, amino groups (which are meant to
include amines that are unsubstituted or mono- or di-
substituted with, for example, alkyl or aryl groups),
alkoxy groups, hydroxy groups, and acid groups (which are
20 meant to include, carboxylic and sulfonic free acids,
acid salts, acid esters, acid amides, and the like).
Examples of such compounds include those in which each of
R⁵⁴, R⁵⁵, and R⁵⁶ are H and R⁵⁸ is an amino group, such as
an unsubstituted amino group. R⁶² represents an alkyl

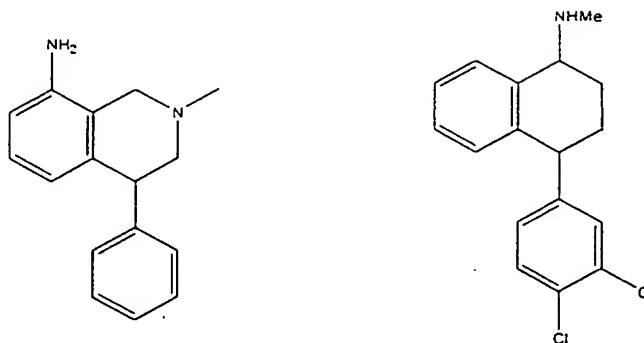
moiety, examples of which include methyl, ethyl, or propyl groups, which can optionally be substituted with, for example, aryl groups (optionally containing a heteroatom) (e.g., pyrid-4-ylmethyl) or amino groups
 5 (which are meant to include amines that are unsubstituted or mono- or di-substituted with, for example, alkyl or aryl groups) (e.g., 2-(N,N-diisopropylamino)ethyl). Alternatively, R^{65} and R^{62} together represent the atoms necessary to complete a 5-12 membered, in which case the
 10 compound produced has the formula ("Formula XLIX"):



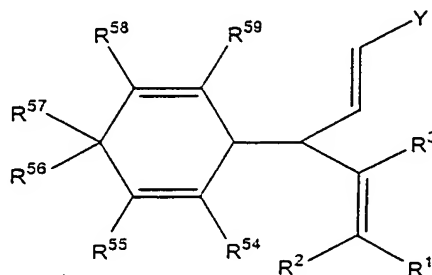
In this formula, Z^6 represents, for example, an alkylene group (e.g., a group having the formula $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(NH_2)CH_2CH_2-$, $-CH_2CH_2CH(NH_2)-$, $-CH_2NRCH_2-$,
 15 $-CH_2CH(C_6H_5)CH_2-$, etc.). Specific compounds of Formula XLVIII which can be made using this method include 1,1-diarylalkanes, such as the pharmaceuticals tolterodine and CDP-840, which respectively have the formulae:



as well as nomifensine and sertraline, which respectively have the formulae:



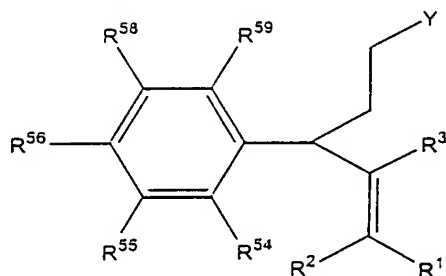
The method includes providing a cyclohexadiene derivative
5 having the formula ("Formula L"):



where R⁵⁷ is H, R⁵⁹ is selected from the group consisting of H, alkyl groups, aryl groups, halogens, amino groups, alkoxy groups, hydroxy groups, and acid groups, and Y is
10 an electron withdrawing group. The choice of R⁵⁹ depends upon whether, in the intended product of Formula XLVIII, R⁶⁵ represents an H, an alkyl group, an aryl group, a halogen, an amino group, an alkoxy group, a hydroxy group, or an acid group or whether R⁶⁵ combines with R⁶²
15 to represent a ring structure. In the former case, R⁵⁹ is most conveniently selected so as to be the same as the desired R⁶⁵ group. In the latter case, R⁵⁹ is chosen to be suitably reactive with a cyclizing agent (e.g., R⁵⁹ can be hydrogen). Cyclohexadiene derivatives which can
20 be used in this reaction are those described above, and

they can be conveniently prepared using, for example, the methods disclosed above.

Once the cyclohexadiene derivative having Formula L is provided, it is converted with hydrogenating and oxidizing agents under conditions effective to form a phenyl derivative having the formula ("Formula LI"):

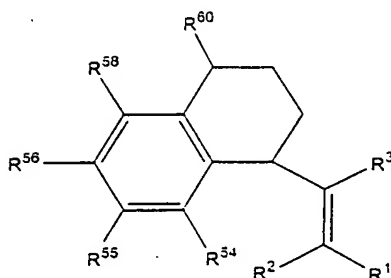


The hydrogenation and oxidation reactions can be carried out simultaneously or sequentially, and, when carried out sequentially, hydrogenation can precede oxidation or oxidation can precede hydrogenation. Suitable hydrogenating and oxidizing agents and methods for their use are described above with regard to methods for preparing compounds having Formula XLIV.

The phenyl derivative having Formula LI is then converted to the compound having Formula XLVIII. Conditions effective for achieving this conversion depends on the nature of the desired substituents at R⁶² and R⁶⁵. Generally, in the case where R⁶² and R⁶⁵ are discreet moieties (i.e., in the case where R⁶² and R⁶⁵ do not combine to form a ring structure), R⁵⁹ will have been chosen so that no further chemistry is required at that position to obtain the desired R⁶⁵ substituent, and the -CH₂CH₂Y moiety can be converted to the desired R⁶² substituent using conventional methods. In the case where R⁶² and R⁶⁵ combine to form a ring, conventional cyclization chemistry can be employed. For example, in the case where R⁵⁹ is H and R⁶² and R⁶⁵ together represent a -CH₂CH₂CH₂- moiety, cyclization can be carried out

using, for example, a Friedel-Crafts acylation catalyst, such as those described in Larock, particularly at pp. 1381-1403, which is hereby incorporated by reference.

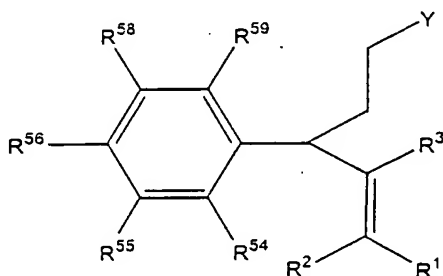
The above method for making compounds having Formula XLVIII is illustrated by the following procedure for making sertraline or sertraline congeners having the formula ("Formula LII"):



In Formula LII, R^1 , R^2 , R^3 , R^{54} , R^{55} , R^{56} , and R^{58} are defined as they were above with regard to compounds of Formula XXXVII. R^{60} is H. R^{61} can represent a substituted or unsubstituted amine, such as an amine having the formula $-NR^{63}R^{64}$, where each of R^{63} and R^{64} is independently selected from hydrogen, an alkyl group, and an aryl group. Illustratively, R^{61} can be a dialkyl amino group (e.g., $N(CH_3)_2$), a monoalkylamino group (e.g., $-NHCH_2CH_3$), or a monoarylamino group (e.g., $-NH(C_6H_5)$), or R^{61} can represent a cyclic amine moiety, such as a piperidinyl group or a morpholino group. Alternately, R^{60} and R^{61} , together with the carbon atom to which they are bonded, can represent a carbonyl (i.e., a $C=O$) moiety.

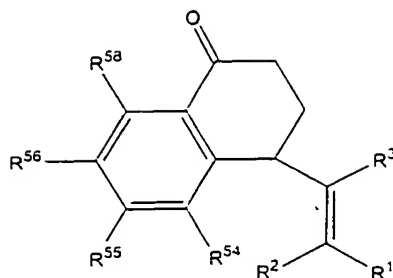
The method includes providing a cyclohexadiene derivative having Formula XXXVII in which Y is an electron withdrawing group, such as any one of the electron-withdrawing groups described above, and R^{57} and R^{59} are H. Cyclohexadiene derivatives which can be used in this reaction are those described above. Once the cyclohexadiene derivative is provided, it is converted

with hydrogenating, oxidizing, and cyclizing agents under conditions effective to form the compound of Formula LII. The hydrogenation and oxidation reactions can be carried out simultaneously or sequentially, and, when carried out sequentially, hydrogenation can precede oxidation or oxidation can precede hydrogenation. Generally, it is desirable that both hydrogenation and oxidation precede cyclization, that is, that the cyclohexadiene derivative be converted with a hydrogenating agent and an oxidizing agent into a phenyl derivative having the formula ("Formula LIII"):



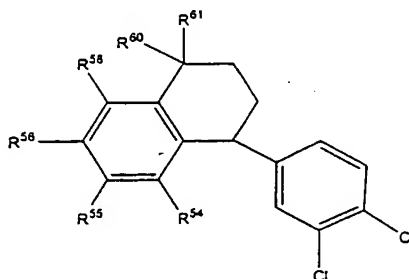
and that the phenyl derivative then be converted with a cyclizing agent under conditions effective to produce the compound.

Suitable hydrogenating and oxidizing agents and methods for their use are described above with regard to methods for preparing compounds having Formula XLIV. Cyclizing agents suitable for use in the practice of the present invention include acylation catalysts, such as Friedel Crafts acylation catalysts, examples of which include ClSO_3H , AlCl_3 , and other Lewis acids. In the case where Y is an alkoxycarbonyl group, it may be advantageous to convert the alkoxy group to a hydroxy group, prior to treatment with the Friedel Crafts acylation catalyst. This can be done using strong acid, e.g., 6 N HCl , or by any other suitable method. The immediate product of such a cyclization is a tetralone having the formula:

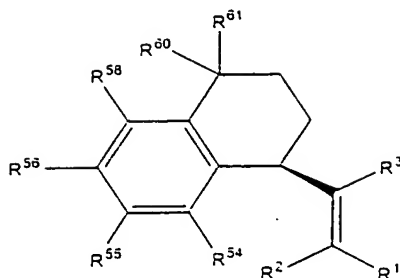


which can be readily converted to compounds having
Formula LII by methods known to those skilled in the art,
such as the reductive amination method set forth in
5 Corey, which is hereby incorporated by reference.

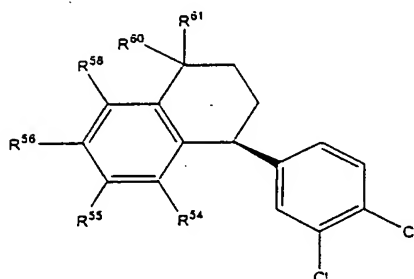
The above-described method is particularly
useful for making compounds having Formula LII in which Y
is an alkoxycarbonyl group (e.g., in which Y has the
formula $-\text{COOR}^{12}$ and R^{12} is an alkyl group) and/or in which
10 R^1 and R^3 , together with the atoms to which they are
bonded, form an aromatic ring, such as a 3,4-
dichlorophenyl ring, in which case the compound of
Formula LII has the formula ("Formula LIV"):



15 Furthermore, by using a cyclohexadiene having Formula
XLII (e.g., a cyclohexadiene having Formula XLIII),
substantially diastereomerically pure compounds of
Formula LII, such as those having the formula ("Formula
LV"):



and, more particularly, those having the formula
("Formula LVI"):



5 can be prepared.

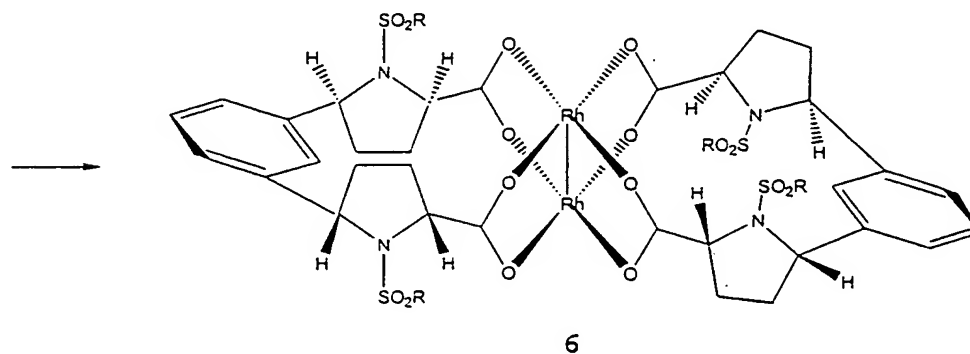
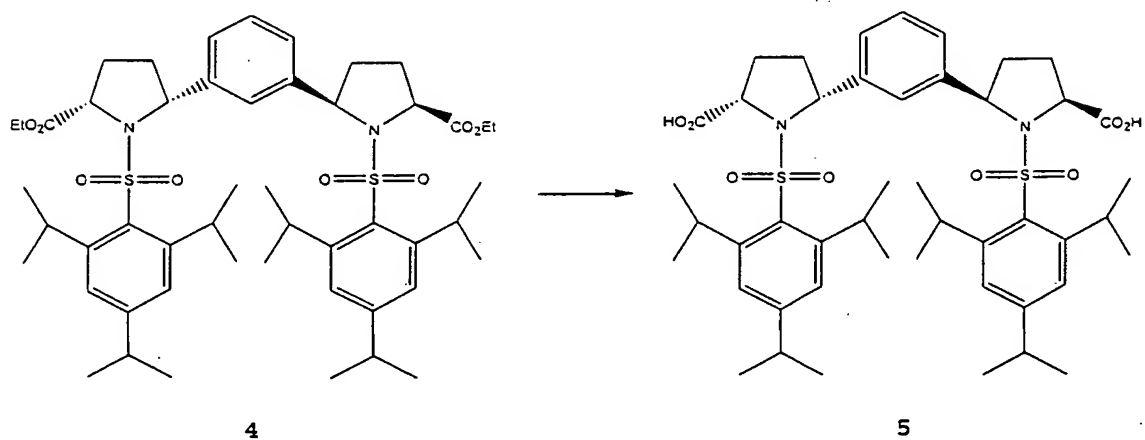
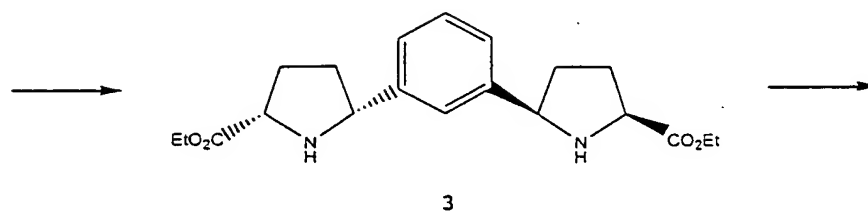
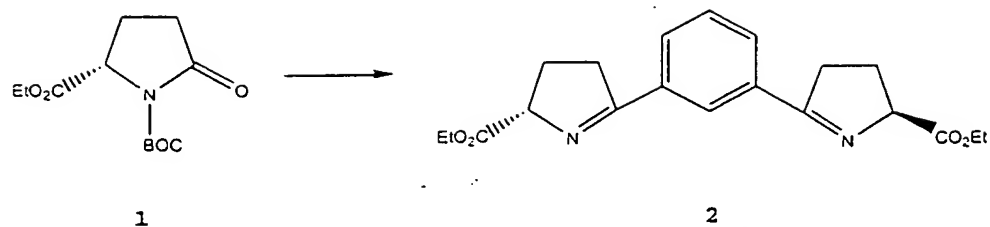
The present invention is further illustrated by
the following non-limiting examples.

EXAMPLES

10 Example 1 -- Synthetic Scheme for the Preparation of
Dirhodium Bis[bridged-di(*S*-2,4,6-triisopropylphenyl-
sulfonylprolinate)]

15 Dirhodium bis[bridged-di(*S*-2,4,6-triisopropyl-
phenylsulfonylprolinate)] was prepared using the
following general reaction Scheme I, in which R.
represents a 2,4,6-triisopropylphenyl group. Details for
each step set forth in this scheme are described, below,
in Examples 2-6.

SCHEME I



Example 2 -- Preparation of Imine 2

To a -78°C solution of 1,3-diiodobenzene (3.431 g, 10.4 mmol) in THF (100 ml) was added 1.7 M *t*-butyl lithium (25.1 ml, 42.6 mmol, 4.1 equiv). The mixture was stirred at -78 °C for 0.5 hours and then allowed to warm to room temperature over 1 hour. The mixture was then cooled to -78°C again and then added to a -78°C solution of *S*-*N*-BOC-pyroglutamic ethylester (1) (13.62 g, 62.4 mmol, 6.0 equiv) in THF (75ml). The resulting mixture was stirred at -78°C for 1 hour and then stirred at room temperature for 20 hours. The reaction mixture was poured into water (300 ml), and extracted with ethyl acetate. The organic layer was separated and dried with MgSO₄, and the solvent was removed to produce a residue.

The residue was dissolved in dichloromethane (60 ml). To this was added TFA (48.1 ml, 0.624 mol), and the resulting mixture was stirred at room temperature for 20 hours. The solvent was then removed, and the residue was redissolved in dichloromethane and then extracted four times with saturated bicarbonate, twice with water, and then with brine. The organic layer was separated and dried with MgSO₄, and solvent was removed. The resulting residue was purified by chromatography on silica using EtOAc/hexanes (5:4) to give 1.3827 g of imine 2 as an oil (37%): TLC R_f 0.33 (EtOAc/hexanes (70:30)); [α]²⁵_D=109° (c 1.358, CHCl₃); IR (NaCl) 2981, 1738, 1623, 1576 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.31 (s, 1H), 7.95 (d 2H), 7.43 (t, 1H), 4.88 (dd, 2H, *J* = 7.6, 7.2 Hz), 4.21 (q, 4H, *J* = 7.6 Hz), 3.22-3.08 (m, 2H), 3.04-2.90 (m, 2H), 2.40-2.27 (m, 2H), 2.27-2.13 (m, 2H), 1.29 (t, 6H, *J* = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 174.7, 171.9, 133.3, 129.5, 127.7, 126.7, 73.8, 60.1, 34.6, 25.6, 13.3. HRMS (EI) calcd for C₂₀H₂₄N₂O₄, 356.1736, found 356.1718.

Example 3 -- Preparation of Diamine 3

Imine 2 (2.4236 g, 6.80 mmol) was hydrogenated at 55 psi of H₂, with PtO₂ (6 mg/mmol of substrate) in ethanol (6 ml/mmol of substrate). The reaction was
5 agitated for 25 hours and then filtered through a plug of celite. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica using EtOAc/hexanes (2:1 w/5% triethylamine) to give 2.196 g of diamine 3 as an oil (90%): TLC R_f 0.31
10 (EtOAc/hexanes (2:1 w/5% triethylamine)); $[\alpha]^{24}_D = 11^\circ$ (c 3.794, CHCl₃); IR (NaCl) 3356, 2983, 2908, 2876, 1742, 1731, 1609, 1454, 1380 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.45 (s, 1H), 7.40-7.25 (m, 3H), 4.30-4.10 (m, 6H), 3.90 (dd, 2H, J = 8.4, 8.1 Hz), 2.42 (s, 2H), 2.30-2.05 (m,
15 6H), 1.92-1.60 (m, 2H), 1.30 (t, 6H, J = 7.5 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 174.8, 143.2, 128.3, 125.2, 125.1, 63.2, 60.6, 59.7, 33.8, 30.2, 13.9; HRMS (EI) calcd for C₁₇H₂₃N₂O₂(m-COOEt), 287.1757, found 287.1723.

Example 4 -- Preparation of Bridged di(ethyl S-2,4,6-
20 triiso-propylphenylsulfonylprolinate) 4

Diamine 3 (1.4 g, 3.95 mmol) and potassium carbonate (2.2 g, 15.8 mmol, 4.0 equiv) were stirred in acetone (40 ml). Then, 2,4,6-triisopropylbenzenesulfonyl chloride (3.6 g, 11.8 mmol, 3.0 equiv) was added. After
25 the resulting reaction mixture was stirred for four (4) days at room temperature, a second portion of acetone (100 ml) was added. The mixture was filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica using
30 EtOAc/hexanes (1:9) to give 2.1 g of bridged di(ethyl S-2,4,6-triiso-propylphenylsulfonylprolinate) ("diTipBSP-

COOEt") 4 as a white solid (mp 57-59 °C) (59%): TLC R_f 0.16 (EtOAc/Hexanes (10:90)); $[\alpha]^{25}_D = -21^\circ$ (c 2.188, CHCl₃); IR (NaCl) 2963, 2868, 2263, 1753, 1600, 1563, 1463, 1316, 1153 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.60 (d, 2H, $J = 7.8$ Hz), 7.28-7.20 (m, 2H), 7.07 (s, 4H), 5.13 (t, 2H, $J = 6.3$ Hz), 4.53 (dd, 2G, $J = 7.2, 4.8$, Hz), 4.16-3.82 (m, 8H), 2.84 (sept, 2H, $J = 6.9$ Hz), 2.50-2.00 (m, 8H), 1.19 (d, 12H, $J = 6.9$ Hz), 1.18 (d, 12H, $J = 6.3$ Hz), 1.12 (d, 12H, $J = 6.9$ Hz), 1.01 (t, 6H, $J = 7.1$ Hz); ¹³C NMR (75 MHz, CDCl₃) δ 171.8, 153.3, 151.8, 151.7, 141.3, 130.4, 127.8, 126.8, 126.1, 123.5, 63.8, 61.0, 60.7, 35.4, 33.9, 29.9, 29.2, 24.8, 24.5, 23.3, 13.7; Anal. Calcd for C₅₀H₇₂N₂O₃S₂: C, 67.23, H, 8.12, N, 3.13, Found: C, 66.99, H, 8.19, N, 3.08.

15 Example 5 -- Preparation of Bridged di(S-2,4,6-triisopropylphenylsulfonylproline) 5

diTiPBSP-COOEt 4 (2.1 g, 2.33 mmol) was dissolved in THF (12 ml), and, then, H₂O (6 ml), LiOH.H₂O (323 mg, 7.69 mmol, 3.3 equiv), and ethanol (6 ml) were added. The reaction was stirred at room temperature for five (5) hours, and, then, it was acidified with 0.5 N HCl to a pH of 2. The acidified mixture was extracted with dichloromethane and separated. The organic layer was dried with Na₂SO₄, and the solvent was removed to give a solid. The solid was purified by recrystallization with chloroform/hexanes to give 2.07 g of bridged di(S-2,4,6-triisopropylphenylsulfonylproline) ("diTiPBSP-COOH") 5 as a white solid (mp 86-88°C) (Quantitative): $[\alpha]^{25}_D = 116^\circ$ (c 1.256, CHCl₃); IR (NaCl) 3062, 2961, 2929, 2876, 2759, 2648, 2569, 2261, 1726, 1604, 1561, 1460, 1434, 1365, 1317, 1248, 1158 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 11.07 (s, 2H), 7.70 (s, 1H), 7.20-6.95 (m, 5H), 6.81 (s, 2H), 4.93

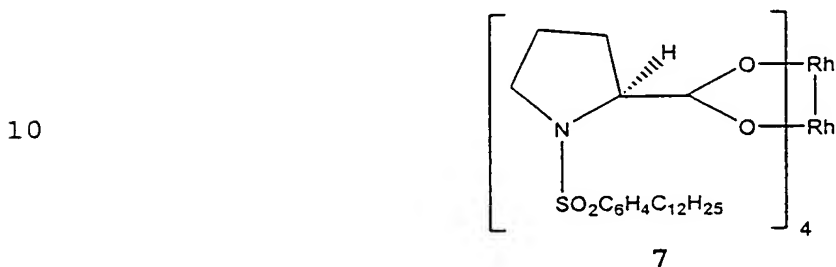
(t, 2H, $J = 6.3$ Hz), 4.73 (t, 2H, $J = 6.5$ Hz), 3.98 (sept, 4H, $J = 6.6$ Hz), 2.82 (sept, 2H, 6.6 Hz), 2.60-2.00 (m, 8H), 1.18 (d, 12H, $J = 6.6$ Hz), 1.12 (d, 12H, $J = 6.3$ Hz), 0.99 (d, 12H, $J = 6.6$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 178.3, 153.6, 151.7, 141.1, 129.9, 127.6, 126.7, 126.4, 123.5, 64.2, 60.1, 34.1, 33.9, 30.4, 29.2, 29.1, 24.7, 24.6, 23.3; Anal Calcd. for $\text{C}_{46}\text{H}_{54}\text{N}_2\text{O}_3\text{S}_2$: C, 66.00, H, 7.71, N, 3.35, Found: C, 65.71, H, 7.93, N, 3.22.

10 Example 6 -- Preparation of Dirhodium Bis[bridged-di(S-2,4,6-triisopropylphenylsulfonylprolinate)] 6

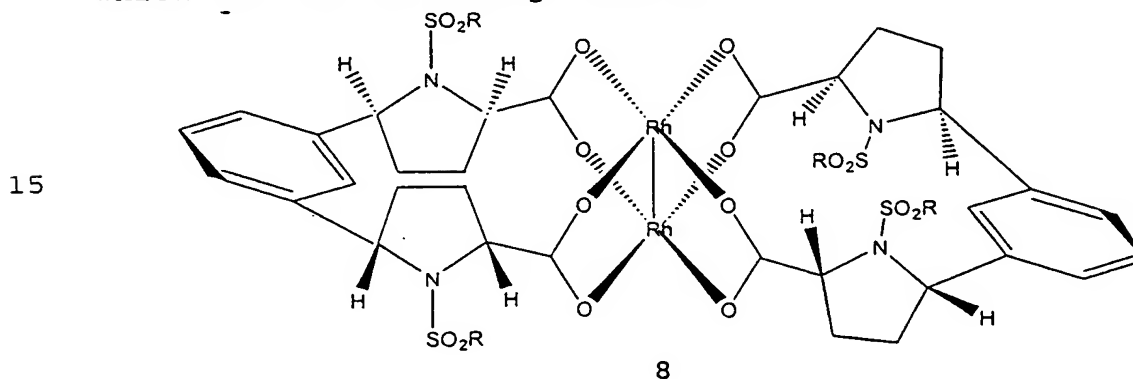
diTiPBSP-COOH 5 (1.00 g, 1.2 mmol) and rhodium acetate (240 mg, 0.54 mmol) were dissolved in chlorobenzene (35 ml). The solution was refluxed through a soxhlet extractor containing calcium carbonate for 72 hours. The solution was then cooled, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica using EtOAc/hexanes (1:9) to give 484 mg of dirhodium bis[bridged-di(S-2,4,6-triisopropylphenyl-sulfonylprolinate)] as a green solid (48%): TLC R_f 0.18 (EtOAc/hexanes (10:90)); IR (NaCl) 2966, 2929, 2871, 1603, 1417, 1321, 1161 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.10 (s, 8H), 6.97 (t, 2H, $J = 7.4$ Hz), 6.81 (d, 4H, $J = 8.4$ Hz), 6.80 (s, 2H), 4.63 (t, 4H, $J = 8.2$ Hz), 4.39 (d, 4H $J = 7.6$ Hz), 3.47 (sept, 8H, $J = 6.4$ Hz), 2.96 (sept, 4H, $J = 6.8$ Hz), 2.41 (dd, 4H, 12.2, 6.0 Hz), 2.24-2.14 (m, 4H), 2.14-2.00 (m, 4H), 1.76-1.63 (m, 4H), 1.31 (d, 12H, $J = 6.8$ Hz), 1.29 (d, 12H, $J = 6.8$ Hz), 1.05 (d, 24H, $J = 6.8$ Hz), 0.94 (d, 24H, $J = 6.0$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 190.5, 153.1, 151.4, 141.6, 130.5, 127.1, 127.0, 124.7, 123.6, 64.7, 62.3, 34.9, 34.0, 29.3, 27.8, 25.0, 24.6, 23.5; HRMS (FAB) calcd for $\text{C}_{92}\text{H}_{125}\text{N}_4\text{O}_{16}\text{S}_4\text{Rh}_2$ 1875.6084, found 1875.6076.

Example 7 -- Regio-, Diastereo-, and Enantio-selective C-H Insertions of Aryldiazoacetates Into Cyclic N-BOC Protected Amines

This example demonstrates that highly regio-
 5 diastereo- and enantioselective C-H insertions of
 aryldiazoacetates into cyclic N-BOC protected amines can
 be achieved by using dirhodium tetrakis(*S*-4-dodecylphenylsulfonylprolinate) (" $\text{Rh}_2(\text{S-DOSP})_4$ "), which
 has the following formula:



and by using dirhodium bis[bridged-di(*S*-4-*t*-butylphenylsulfonylprolinate)] (" $\text{Rh}_2[\text{bridged}(\text{S-TBSP})_2]_2$ "), which has the following formula:

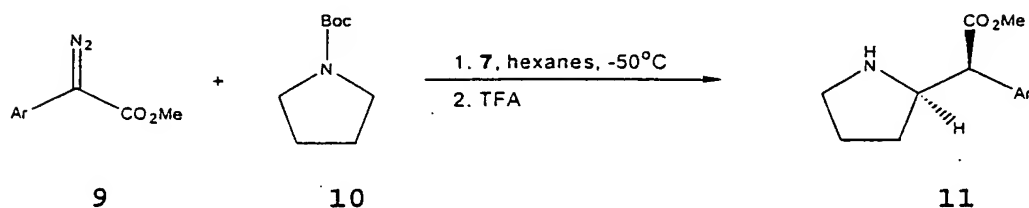


in which each R represents a 4-*t*-butylphenyl group.
 $\text{Rh}_2(\text{S-DOSP})_4$ was purchased commercially from Aldrich, and
 $\text{Rh}_2[\text{bridged}(\text{S-TBSP})_2]_2$ was made using the procedures set
 20 forth in Examples 1-6, above, except that diamine 3 was

reacted with 4-*t*-butylbenzenesulfonyl chloride instead of 2,4,6-triisopropylbenzenesulfonyl chloride.

The highly regio-, diastereo-, and enantioselective C-H insertion of aryldiazoacetates into cyclic N-BOC protected amines was carried out using Rh₂(S-DOSP)₄ in the following reaction Scheme II:

SCHEME II



Briefly, methyl phenyldiazoacetate (9, Ar = phenyl) was prepared from methyl diazoacetate by the general method set forth in Davies et al., "Direct Synthesis of Furans From Rhodium(III) Stabilized Carbenoids With Alkenes," Org. Synth., 70:92-99 (1991), which is hereby incorporated by reference. To 5 ml of hexanes were added of N-BOC pyrrolidine (10) (0.351 g, 2 mmol, 2 equiv) and Rh₂(S-DOSP)₄ (0.019 g, 0.01 mmol, 0.01 equiv). The mixture was chilled to -50° C, and methyl phenyldiazoacetate (0.176 g, 1 mmol, 1 equiv) in 10 ml hexanes was added. The mixture was stirred for 12 hours and then warmed slowly to room temperature. The solvent and excess N-*tert*-butyl-pyrrolidine carboxylate were removed on a rotary evaporator and by kugelrohr distillation. The crude product was treated with TFA (10 equiv) at room temperature for one hour and was thrice extracted with water. The aqueous phase was basified to pH 10-11 with NaHCO₃ and thrice extracted with methylene chloride. The combined organic layers were dried with MgSO₄ and concentrated to give the free amine (11 (Ar =

phenyl)) in 96:4 dr (by ^1H -NMR). To calculate yield, the free amine (11 (Ar = phenyl)) was converted to its hydrochloride salt by dissolving the free amine in ethyl ether (5 ml), adding an excess of a 1 M HCl/diethyl ether solution, filtering the resulting precipitate, washing the collected solid with diethyl ether, and drying the resulting white solid. The overall yield was 183 mg or 72 %.

In like manner, the above reaction was repeated for other methyl aryldiazoacetates, and the results are presented in Table I, below:

TABLE I

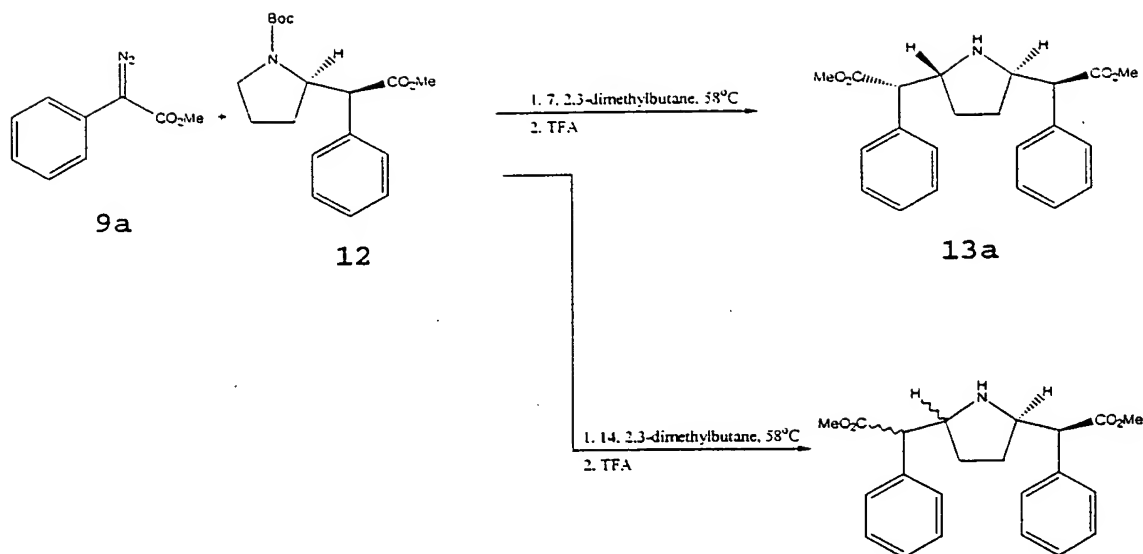
	Ar	yield, %	ee, %	de, %
a	Ph	72	94	92
b	p-Cl-Ph	70	94	94
c	p-Me-Ph	67	93	94
d	2-Naphthyl	49	93	92

In Table I, the diastereoselectivity of the formation of 11 was determined from the ^1H NMR of the crude amine after extraction and removal of solvent. The yields for 11a and 11c-11e represent the amounts of crystalline hydrochloride salt that was obtained after treating the crude amine with ethereal HCl. The yield of 11b represents the pure amine after purification by column chromatography. The enantioselectivity was determined by conversion of the crude amine to its trifluoroacetamide derivative followed by chiral HPLC or GC analysis. The relative stereochemistry of 11c was readily determined by converting 11c to a fused β -lactam in which the cis arrangement of the 2 protons in the β -lactam ring was assigned on the basis of a distinctive coupling ($J = 5.1$

Hz) and nOe experiments (Coulton et al., Chem Soc. Perkin
Trans. I, 1998:1193-1202, which is hereby incorporated by
reference). The absolute stereochemistry of 11a was
determined to be (2*S*, 2'*R*) using the Mosher amide method
5 described in Hoye et al., Org. Chem., 61:8489-8495
(1996), which is hereby incorporated by reference.

The next issue that was examined was whether a
second C-H insertion was a feasible process. The
reactions and results are summarized in Scheme III,
10 below:

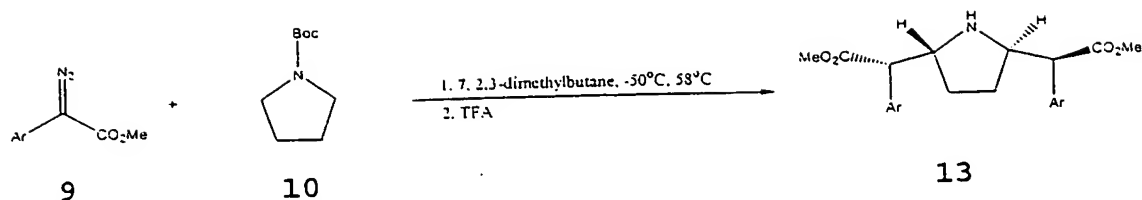
SCHEME III



The reactions were carried out on enantiomerically pure 12 which was obtained from 11a that was first recrystallized as its hydrochloride salt to obtain enantiomerically pure material and then treated with (BOC)₂O. Reaction of 12 with the phenyldiazoacetate 9a (4 equiv) using Rh₂(*S*-DOSP)₄ as catalyst in 2,3-dimethylbutane as solvent resulted in the formation of 13a in 93% yield. The compound was shown to be C₂-symmetric because, in the ¹³C NMR, only 9 signals were apparent. Since the compound is chiral, this rules out the meso diastereomer. In contrast, reaction of 12 with excess 9a using Rh₂(*R*-DOSP)₄ (sometimes denoted "14" hereinafter) as the catalyst, resulted in the formation of mixture of diastereomers and/or regioisomers that were not resolvable.

Further experimentation demonstrated that the C₂-symmetric amines could be formed in a single step, as shown in Scheme IV, below:

SCHEME IV



Briefly, Rh₂(S-DOSP)₄-catalyzed decomposition of 9a (1.5 equiv) at -50°C in the presence of N-BOC-pyrrolidine 10 followed by warming the reaction to 58°C and addition of a further 4.5 equiv of 9a generated the C₂-symmetric amine 13a in 78% yield and 97% ee. Similar bis C-H insertion reactions were carried out with aryldiazoacetates 9b-9e to produce the amines 13b-13e, as summarized in Table II, below:

TABLE II

	Ar	yield, %	ee, %
a	Ph	78	97
b	p-Cl-Ph	50	96
c	p-Me-Ph	51	96
d	2-Naphthyl	62	88
e	p-MeO-Ph	40	97

These amines are appropriately functionalized for further conversion by ester reduction or Grignard addition to highly functionalized and potentially useful C₂-symmetric bases.

Experiments were performed to determine whether it would be feasible to carry out a similar reaction using N-BOC-piperidine, which would provide a direct synthesis of *threo*-methylphenidate (RITALINTM). The

experiments and results are summarized in Scheme V and Table III, below:

SCHEME V

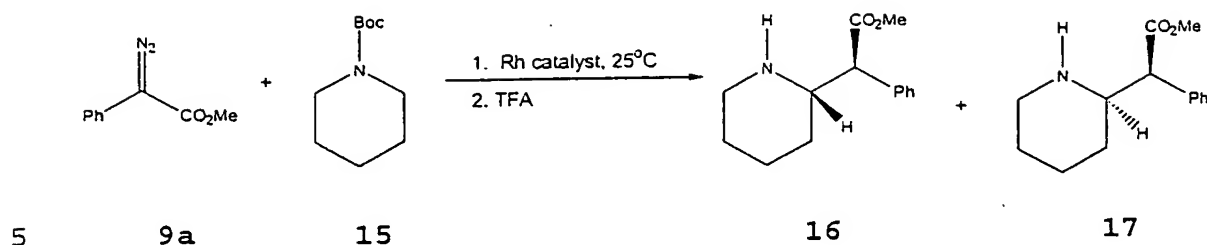


TABLE III

10

Rh catalyst	equiv of 15	16 + 17 yield, %	16:17 ratio	16 ee, %	17 ee, %
7	4.0	49	43:57	34 (2 <i>S</i>)	81 (2 <i>S</i>)
7	0.25	86	50:50	25 (2 <i>S</i>)	79 (2 <i>S</i>)
8	0.25	73	71:29	86 (2 <i>R</i>)	65 (2 <i>R</i>)

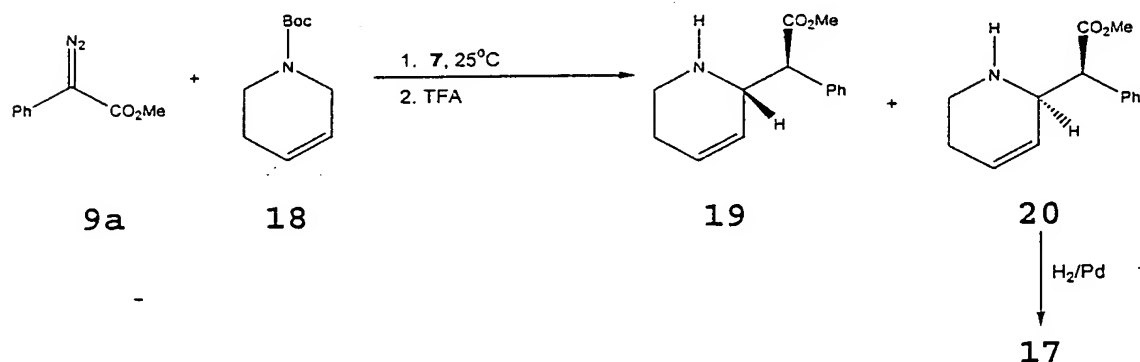
As shown above in Scheme V and Table III, Rh₂(*S*-DOSPP)₄ 7 catalyzed decomposition of methyl phenyldiazoacetate 9a in the presence of N-BOC-piperidine (15, 4 equiv) in 2,3-dimethylbutane at room temperature followed by treatment with trifluoroacetic acid resulted in the formation of a mixture of *threo* and *erythro* methyphenidate, 16 and 17, in 49% yield. However, the *threo* isomer 16 was the minor diastereomer and was formed in only 34% ee. The combined yield of 16 and 17 was improved to 86% by using the N-BOC-peperidine as the limiting reactant. This result is different to what was observed with N-BOC-pyrrolidine, which gave bis C-H insertion when an excess of phenyldiazoacetate was used. A major improvement in enantioselectivity and diastereoselectivity was achieved

25

by carrying out the reaction with the $\text{Rh}_2[\text{bridged}(\text{S-TBSP})_2]_2$ 8 catalyst. The ratio of 16:17 (73% yield) was improved to 2.5:1 and (2*R*, 2'*R*)-*threo* isomer 16 was formed in 86% ee and 52% isolated yield. As shown in Table III, $\text{Rh}_2[\text{bridged}(\text{S-TBSP})_2]_2$ 8 results in opposite asymmetric induction to $\text{Rh}_2(\text{S-DOSP})_4$ 7, and, in the reaction of 9a and 15 catalyzed by 8, the biologically active enantiomer of *threo*-methylphenidate is formed.

The *erythro* diastereomer of methylphenidate 17 was produced by carrying out the reaction with dihydropyridine 18 as illustrated in Scheme Va, below:

SCHEME Va



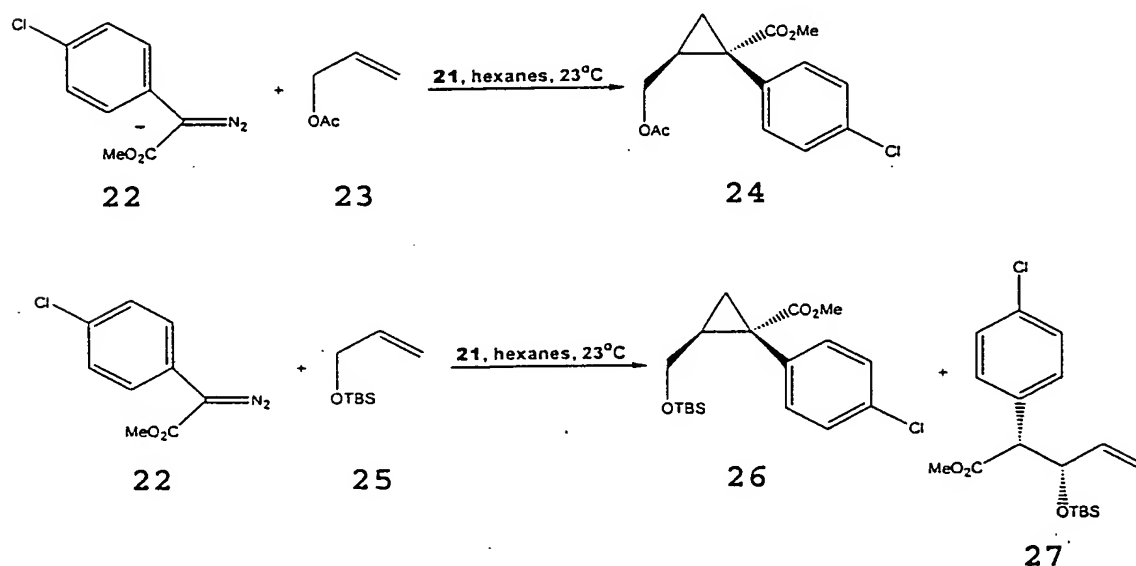
Referring to Scheme Va, $\text{Rh}_2(\text{S-DOSP})_4$ catalyzed decomposition of 9a in the presence of 18 (4 equiv) in 2,3-dimethylbutane at room temperature followed by treatment with TFA resulted in a 63% yield of C-H insertion products 19 and 20. The *erythro* diastereomer 20 was the major diastereomer (62% de) and was isolated in 53% yield and 80% ee. Determination of the relative and absolute stereochemistry of 20 as (2*S*, 2'*R*) was readily achieved by converting 20 to *erythro*-

Example 8 -- Intermolecular C-H Insertion Reactions
Between Allyl Silyl Ethers and Methyl Aryldiazoacetates

5 This example describes further studies to
explore the scope of the asymmetric intermolecular C-H
insertion with particular emphasis on the
chemoselectivity and diastereoselectivity of the
reaction.

10 Simple allyloxy substrates and $\text{Rh}_2[(\pm)\text{-DOSP}]_4$,
(sometimes denoted "21" hereinafter) as catalyst were
initially used to study the selectivity of the C-H
insertions. These reactions are summarized in Scheme VI,
below:

15 SCHEME VI



In the case of the reaction of 4-chlorophenyldiazoacetate 22 with allyl acetate 23 (2 equiv) at room temperature, cyclopropanation was the exclusive reaction, and 24 was

formed in 75% yield. In contrast, in the reaction of 22 with allyl silyl ether, the C-H insertion product 27 was the major product, and, remarkably, it was formed in >94% de. Interestingly, it appears that the $\text{Rh}_2[(\pm)\text{-DOSP}]_4$ catalyst has a major influence on the product distribution because, when the reaction is carried out with dirhodium tetraoctanoate, $\text{Rh}_2(\text{OOct})_4$, as catalyst, the ratio of cyclopropane 26 to C-H insertion product 27 was 2.5:1. No reaction occurred with the dirhodium tetracarboxamide catalyst, $\text{Rh}_2(\text{R-MEPY})_4$ (see Davies, which is hereby incorporated by reference), under these reaction conditions.

The preferential formation of the C-H insertion product 27 is an unprecedented result, because mono-substituted alkenes generally undergo cyclopropanation in high yield on reaction with methyl phenyldiazoacetate. On repeating the reaction with more highly substituted allyl ethers 28, cyclopropanation could be fully eliminated. This is illustrated in Scheme VII and Table IV below:

SCHEME VII

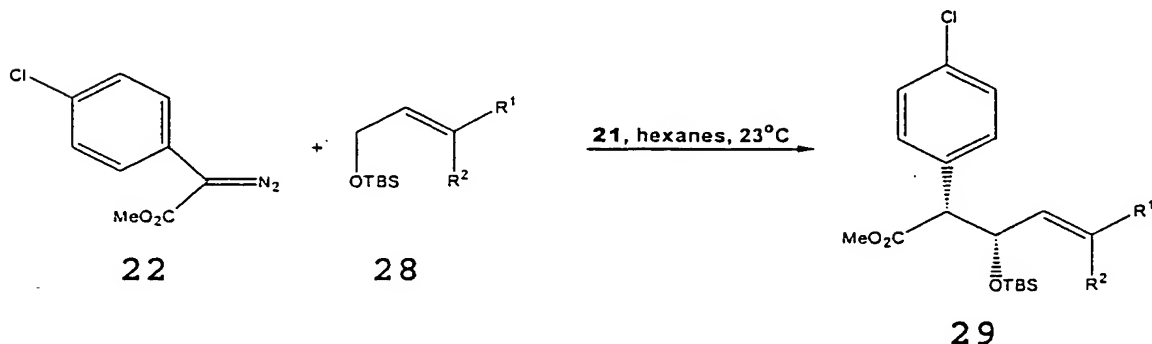


TABLE IV

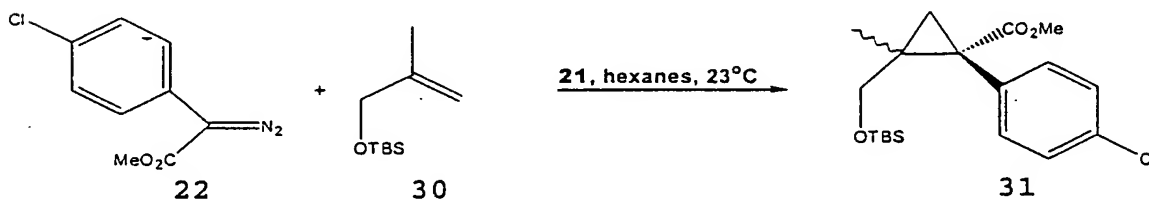
	R ¹	R ²	yield, %	de, %
a	H	Me	48	66
b	Me	Me	44	70
c	Me	H	72	>94

- 5 However, the diastereoselectivity of the C-H insertion was dependent on the allyl ether substitution pattern. With the *trans*-disubstituted or trisubstituted allyl ethers 28a and 28b, the C-H insertion products 29a and 29b were formed with a syn/anti ratio of about 7:1.
- 10 However, with the *trans* disubstituted allyl ether 28c, the C-H insertion product 29c was formed in 72% yield and >94% de.

The steric influences on the C-H insertion versus cyclopropanation can be seen in the reaction with 2-methylpropenyl silyl ether in Scheme VIII, below:

15

SCHEME VIII



- Here, reaction with the 2-methylpropenyl silyl ether 30 results in the formation of the cyclopropane 31 without any evidence showing formation of the C-H insertion product. It is believed that, because the aryldiazoacetate cyclopropanation is nonsynchronous, the silyl ether 30 has an accessible vinyl terminus for cyclopropanation, while the methyl substituent in 30 is presumably interfering with the C-H insertion.
- 20
- 25

Having thus discovered that the trans allyl silyl ether is a promising substrate for diastereoselective C-H insertion, the study was extended to explore the issue of asymmetric induction within this system. $\text{Rh}_2(\text{S-DOSP})_4$ 7 catalyzed decomposition of 22 in the presence of a series of allyl silyl ethers was carried out using the following procedure. A flame dried 50 ml round bottom flask equipped with a magnetic stir bar and a rubber septum was charged with silyl ether (1.5 mmol), $\text{Rh}_2(\text{S-DOSP})_4$ (14 mg, 7.5×10^{-3} mmol), and dry hexane (0.5 ml), and the mixture was stirred under argon at room temperature to give a green solution. A 10 ml gastight syringe was charged with p-chlorophenyldiazoacetate (0.75 mmol) in dry hexane (7.5 ml) to give a 0.10 M diazo solution. Addition via syringe pump was initiated at a rate of 7.5 ml/h (1 h addition time), and the green color of the reaction mixture was maintained during the entire addition. After the diazo addition was complete, the reaction mixture was allowed to stir for an additional hour, and then the solvent and excess silyl ether were removed under reduced pressure. The residue was purified by flash chromatography on silica gel using 96:4 petroleum ether:ether to give the product as a clear oil. The reaction is set forth in Scheme IX, and the results are summarized in Table V below:

SCHEME IX

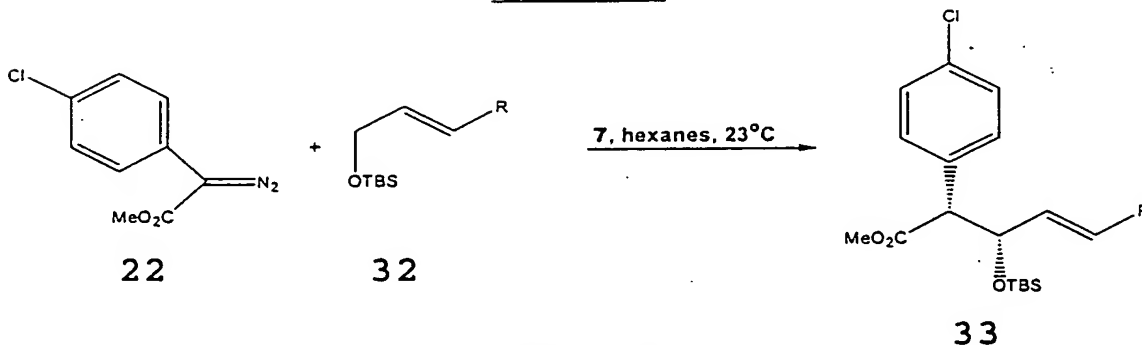


TABLE IV

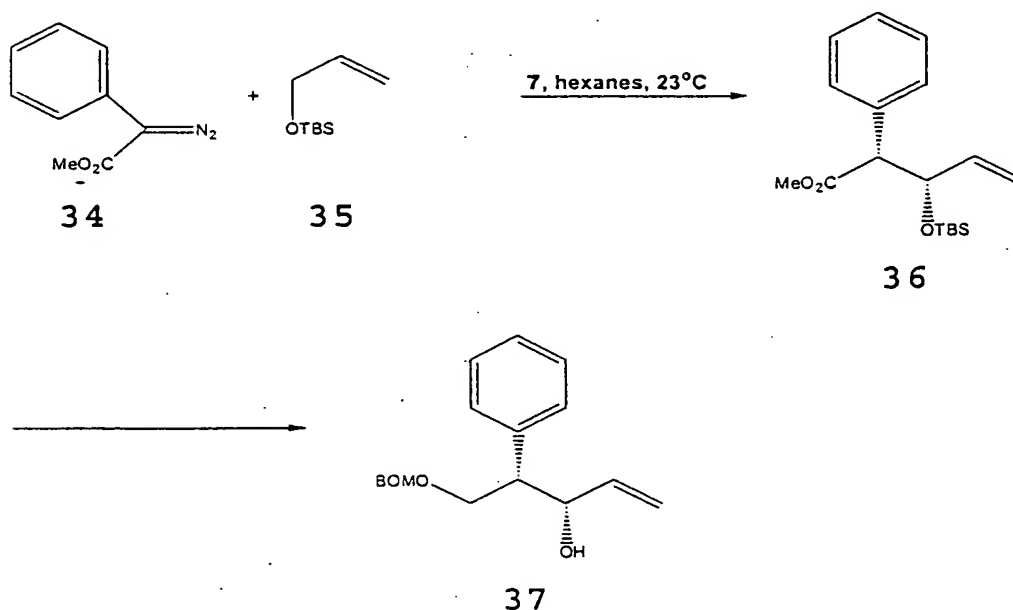
Product	R	yield, %	de, %	de, %
33a	Me	72	>94	80
33b	Ph	55	>94	85
33c	CH=CH ₂	41	>94	74
33d	H	35	>94	90

5

In all instances, the diastereocontrol was >94% de favoring the syn isomer, and the enantioselectivity ranged from 74-90% ee.

In order to determine the absolute stereochemistry of the C-H insertion product, the Rh₂(S-DOSP)₄ catalyzed reaction of methyl phenyldiazoacetate 34 with allyl silyl ether 35 was examined. The reaction is set forth in Scheme X, below:

SCHEME X



15

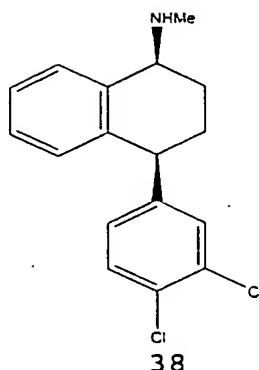
The reaction resulted in the formation of syn isomer 36 as the major product in 52% yield (2.8:1 ratio of 36 to cyclopropane product) and 92% ee. Lithium aluminum hydride reduction of 36, followed by conversion of the

alcohol to its t-butoxymethoxy derivative and silyl deprotection gave 37. The optical rotation of 37 was compared with the value given in Guanti et al., Tetrahedron, 51:10343-10360 (1995), which is hereby
5 incorporated by reference. The absolute stereochemistries of other C-H insertion products are tentatively assigned assuming a similar mode of asymmetric induction for all the substrates.

In summary, these studies, demonstrate that the
10 intermolecular C-H insertions of carbenoids derived from aryl diazoacetates is a practical method for the asymmetric synthesis of products that are typically derived from an aldol reaction. The reaction proceeds with good chemo- and diastereoselectivity, and by using
15 $\text{Rh}_2(\text{R-DOSP})_4$ as catalyst, reasonably high levels of asymmetric induction can be obtained. One particularly attractive feature of this chemistry is the low molar equivalent of catalyst that is required.

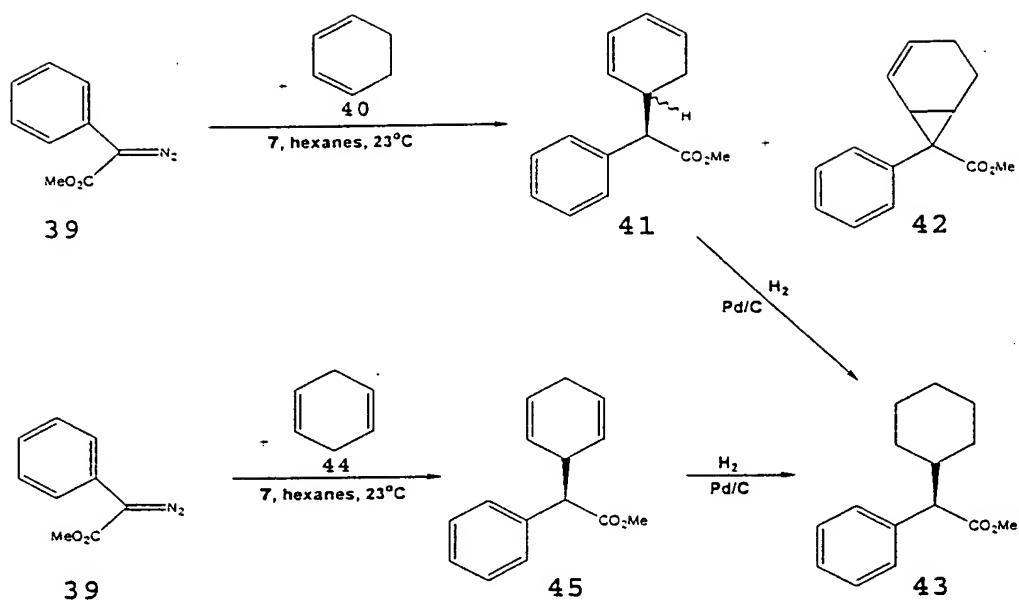
Example 9 -- Catalytic Asymmetric Synthesis of
20 Diarylacetates and 4,4-diarylbutoanoates

This example illustrates a method for the synthesizing diarylacetates and 4,4-diarylbutoanoates using asymmetric carbenoid transformations. The practical utility of this methodology is demonstrated by
25 a short formal synthesis of the antidepressant (-)-sertraline, which has the formula:



Briefly, the method involves reacting methyl
phenyldiazoacetate 39 with 1,3-cyclohexadiene 40 in the
5 presence of $\text{Rh}_2(\text{S-DOSP})_4$ 7, and the reaction
preferentially formed the C-H insertion product 41 rather
than the cyclopropanated product 42. The C-H insertion
product 42 was formed as an inseparable 4:1 mixture of
diastereomers, and, so, in order to determine the extent
10 of the asymmetric induction, 42 was reduced to the known
cyclohexane 43, which was formed in 92% ee (R-
configuration). An even more effective C-H insertion was
achieved on reaction of 39 with 1,4-cyclohexadiene 44, as
this resulted in the formation of the C-H insertion
15 product 45 with very little occurrence of the
cyclopropanation reaction. The absolute stereochemistry
of 45 was determined to be R by reduction of 45 to the
cyclohexane 43 (80% overall yield from 39 with a 91% ee).
These reactions are summarized in Scheme XI, below:

SCHEME XI



The reaction with 1,4-cyclohexadiene could be carried out with a range of aryl diazoacetates 46 as illustrated in Scheme XII and Table VI, below:

SCHEME XII

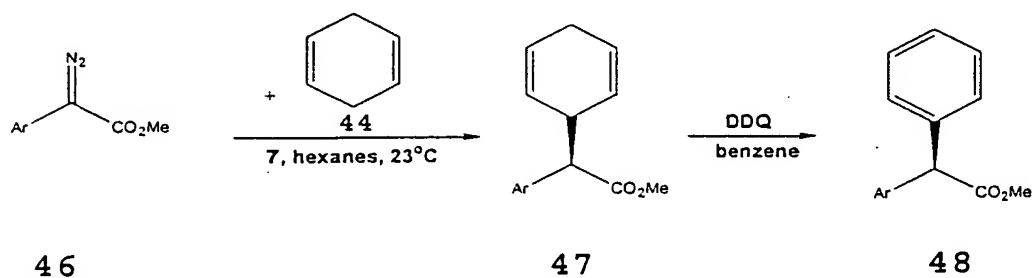


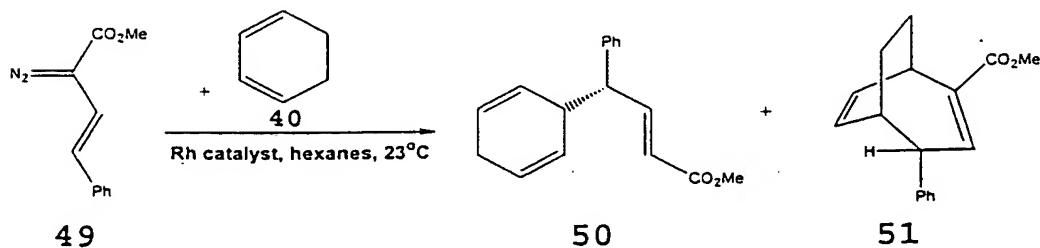
TABLE VI

	Ar	yield 47, %	ee 47, %	yield 48, %	ee 48, %
a	p-Cl-Ph	84	95	86	95
b	p-Me-Ph	84	94	89	94
c	p-MeO-Ph	69	93	87	93
d	2-naphthyl	64	92	88	92

In each case, the C-H insertion product 47 was produced in >90% ee. Furthermore, 47 could be readily oxidized by DDQ to the diarylacetate 48 without racemization. The absolute stereochemistry for 47 and 48 is tentatively assigned on the assumption the asymmetric induction would parallel that observed in the formation of 45.

The new strategy to 4,4-diarylbutanoates was discovered on attempting the C-H insertion reaction with the phenylvinyl diazoacetate 49. Reaction of 49 with 1,3-cyclohexadiene 40 did not result in the formation of the expected C-H insertion product. Instead, the 1,4-cyclohexadiene 50 was formed in 63% yield and 98% ee. A side product in this reaction is the cyclopropanation/Cope rearrangement product 51, as shown in Scheme XIII, below:

SCHEME XIII



The catalyst has a major effect on the product distribution in this reaction, as shown in Table VII, below:

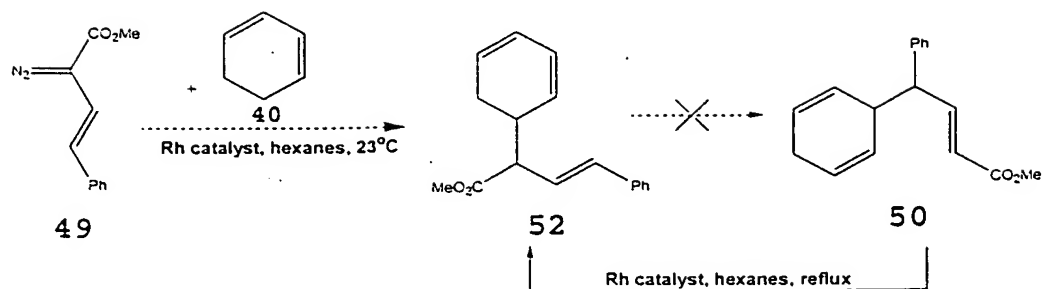
TABLE VII

Rh catalyst	50:51
$\text{Rh}_2(\text{S-DOSP})_4$	86:14
$\text{Rh}_2(\text{OOct})_4$	26:74
$\text{Rh}_2(\text{OPiv})_4$	19:81
$\text{Rh}_2(\text{TFA})_4$	46:54
$\text{Rh}_2(\text{TPA})_4$	30:70

In Table VII, $\text{Rh}_2(\text{OOct})_4$ represents dirhodium(II) tetraoctanoate, $\text{Rh}_2(\text{OPiv})_4$ represents dirhodium(II) tetra(trimethylacetate), $\text{Rh}_2(\text{TFA})_4$ represents dirhodium(II) tetra(trifluoroacetate), and $\text{Rh}_2(\text{TPA})_4$ represents dirhodium(II) tetra(triphenylacetate). For example, when $\text{Rh}_2(\text{OOct})_4$ is used as catalyst, cyclopropanation becomes the preferred reaction. From the range of catalysts that were studied, it appears that catalyst exhibits a subtle combination of steric and electronic effects. At present, $\text{Rh}_2(\text{S-DOSP})_4$ is the best catalyst for limiting the cyclopropanation reaction, resulting in a 84:16 ratio of 50:51.

One possible mechanism for the formation of cyclohexadiene 50 would be an allylic C-H insertion between 49 and 1,3-cyclohexadiene 40 to form 52 which could then undergo a Cope rearrangement to form 50, as shown in Scheme XIV, below:

SCHEME XIV



However, there is no apparent driving force for the Cope rearrangement of **50** and **52**. Indeed, there is evidence
 5 that the driving force for the Cope rearrangement is in the reverse direction by heating **50** in refluxing hexane, because, under these conditions, **50** slowly rearranges to **52**. In view of this, alternative mechanistic possibilities need to be considered. It is conceivable
 10 that **50** is derived by an intercepted C-H insertion process or by means of an ene reaction where the vinylcarbenoid reacts as a 2π system.

The reaction described in Scheme XIII was extended to a range of arylvinyl diazoacetates, as
 15 illustrated in Scheme XV and Table IX, below:

SCHEME XV

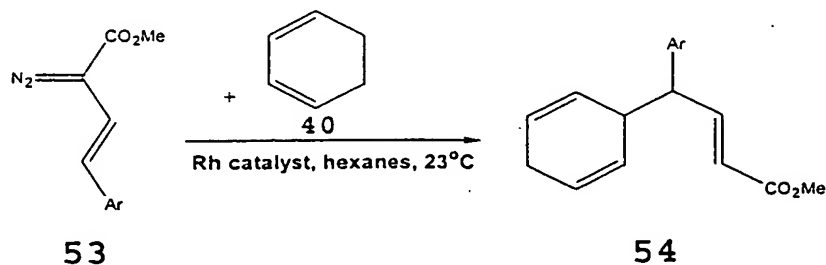


TABLE IX

	Ar	yield 54, %	ee 54, %
a	p-MeO-Ph	58	99
b	3,4-diClPh	59	99
c	2-naphthyl	50	99
d	o-MeO-Ph	17	86
e	1-naphthyl	22	84

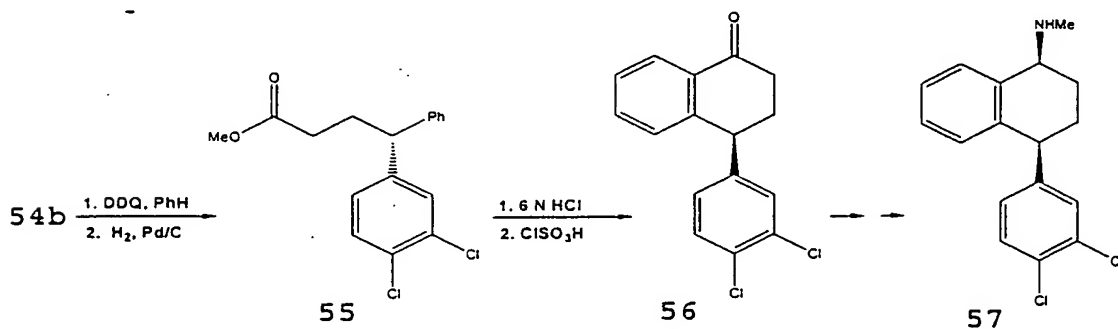
Each of the reactions was performed using the following general procedure, which is illustrated using methyl 3,4-dichlorophenylvinyl diazoacetate 53b as a reactant. A solution of the vinyl diazoacetate 53b (207 mg, 0.764 mmol) in dry hexanes (20 ml) was added dropwise over 15 minutes to a flame-dried flask containing a stirred solution of $\text{Rh}_2(\text{S-DOSP})_4$ (12 mg, 6.4×10^{-3} mmol) and the diene (0.4 ml, 4 mmol) in dry hexane (30 ml) at room temperature. After 16 hours, the solvent was removed under reduced pressure. Purification by flash silica gel column chromatography (petroleum ether/ether, 9:1, R_f = 0.24) gave 54b in 59% yield as a clear oil. 99% ee (determined by HPLC: Daicel-OD, 0.8% *i*-Pr-OH in hexanes, 0.8 ml/min; T_r = 12.06 min (minor), 23.73 min (major)). $[\alpha]^{25}_D = +4^\circ$ (c 2.08, CHCl_3). IR (neat) 3029, 2954, 2863, 2817, 1726, 1651 cm^{-1} ; ^1H NMR (300 MHz) δ 7.36 (d, 1 H, J = 8.0 Hz), 7.27 (d, 1H, J = 2.5 Hz), 7.10 (dd, 1H, J = 15.5 Hz), 7.02 (dd, 1H, J = 8.0, 2.5 Hz), 5.81 (d, 1H, J = 15.5 Hz), 5.75 (Br. d, 2H, J = 12.0 Hz), 5.57 (Br. d, 1H, J = 10.0 Hz), 5.43 (Br. d, 1H, J = 10.0 Hz), 3.71 (s, 3H), 3.38 (dd, 1H, J = 8.5, 8.0 Hz), 3.17-3.15 (m, 1H), 2.62-2.48 (m, 2H); ^{13}C NMR (125 MHz) δ 166.5, 148.1,

140.7, 132.4, 130.8, 130.4, 130.2, 127.6, 126.83, 126.79, 125.7, 125.3, 122.9, 53.6, 51.6, 40.1, 26.3. HRMS calcd for $C_{17}H_{16}O_2Cl_2$, 322.0527, found, 322.0504.

The reactions with *m*- or *p*-substituted benzene (53a, 53b) or 2-naphthyl derivatives (53c) result in the formation of 54a-54c with exceptionally high levels of asymmetric induction (99% ee). In contrast, the reaction with *o*-substituted benzene (53d) and 1-naphthyl (53e) result in the formation of 54d and 54e with lower enantioselectivity (84-86% ee). Also, the yields of 54d and 54e were greatly decreased compared to 54a-54c, because, it is believed, the major product in these last two reactions was the cyclopropanation/Cope rearrangement product, analogous to 51.

The cyclohexadiene 54b is an excellent precursor for the formal synthesis of (-)-sertraline, as illustrated in Scheme XVI, below:

SCHEME XVI



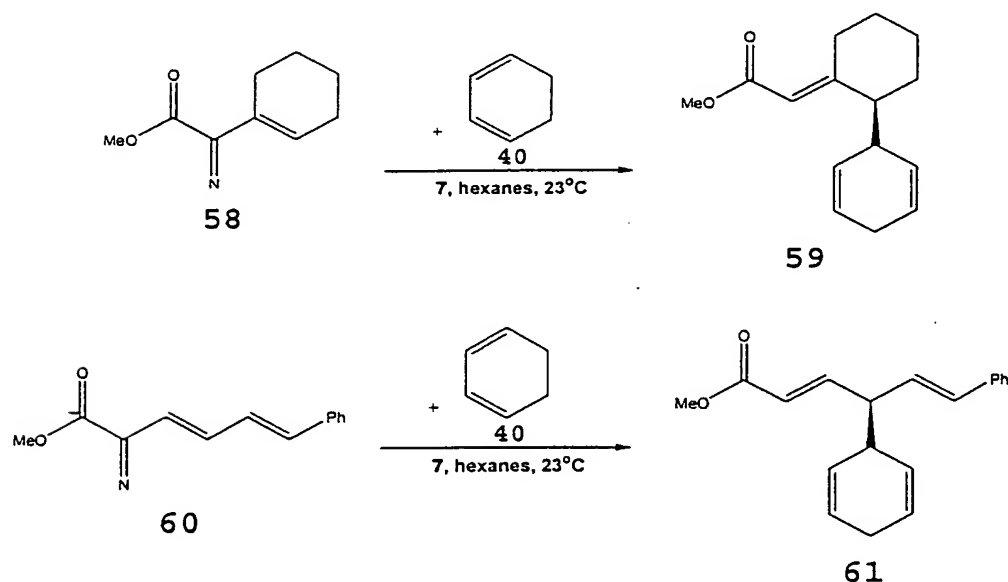
Oxidation of 54b with DDQ followed by catalytic hydrogenation over Pd/C formed the 4,4-diarylbutanoate 55 (52% yield for 3 steps from 53b) with minimal racemization (96% ee). Ester hydrolysis of the 4,4-

diarylbutanoate 55 followed by an intramolecular Friedel-Crafts acylation generated the tetralone 56 in 79% yield for 2 steps. Conversion of the tetralone 56 to (-)-sertraline 57 was carried out following the method
5 described in Corey, which is hereby incorporated by reference.

The general chemistry described in this example is applicable to other vinylcarbenoid systems as illustrated in Scheme XVII, below:

10

SCHEME XVII



$\text{Rh}_2(\text{S-DOSP})_4$ -catalyzed decomposition of the cyclic vinyl diazoacetate 58 in the presence of 1,3-
15 cyclohexadiene 40 resulted in the formation of the 1,4-cyclohexadiene 59 in 73% yield and 97% ee. The absolute configuration of compound 59 was determined by DDQ oxidation and ozonolysis to afford the 2-phenylcyclohexanone in a 56% yield. Found $[\alpha]^{26}_D = -17$

(c = 1.66, PhH). Lit. value: $[\alpha]^{24}_D = -113.5$ (c = 0.60, PhH), S-isomer. (Berti et al., J. Chem. Soc., pp. 3371-3377 (1971), which is hereby incorporated by reference.) Similarly, decomposition of the dienyldiazoacetate 60 in
5 the presence of 1,3-cyclohexadiene 40 resulted in the formation of 61 (60% yield and 99% ee), in which both diene components have moved out of conjugation.

Although the invention has been described in detail for the purpose of illustration, it is understood
10 that such detail is solely for that purpose, and variations can be made therein by those skilled in the art without departing from the spirit and scope of the invention which is defined by the claims which are set forth below.